Variations in Subjective State Over the Oral Contraceptive Pill Cycle

The influence of endogenous steroids and temporal manipulations

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FOR WILMA CROWTHER AND EDWIN ARDENER
WHOM I KNEW TOO LITTLE AND WHO WERE LOST TOO SOON.

I HOPE THIS IS A CREDIT TO YOUR TUTELAGE.

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Declaration

The research described in this thesis was the unaided work of the author, except where indicated by acknowledgement or reference. No part of this work has previously been submitted or accepted for any other degree, nor is any part of it being concurrently submitted in candidature for another degree.

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Abstract

Many biological systems vary rhythmically in response to changes in both the external and internal environment. Some rhythms, such as the menstrual cycle in women, are built into the organism and repeat themselves over time without any support from external factors. It has been acknowledged for a long time that in addition to the predictable changes in steroid hormones that occur over the menstrual cycle, many women also experience concomitant changes in their physical and emotional well being. Most of the literature concentrates on the fact that negative moods and physical changes seem to occur predominantly before and during menstruation. Given the close temporal relationship of these changes to the timing of the steroid cycle, causal mechanisms have traditionally been sought in the hormonal changes themselves. Yet the literature reveals that no causal role has consistently been found for any of a large number of hormonal parameters that change over the menstrual cycle. Further, there is good evidence that variations in well being of a similar magnitude, and with similar timing occur during the combined oral contraceptive pill cycle.

This thesis is concerned with exploring the aetiology of cycle-related change in emotional and physical well being during oral contraceptive use. Its two fundamental objectives are 1) to clarify why women taking the pill have similar experiences to women with hormonally distinct, menstrual cycles, and 2) to test a novel aetiological hypothesis with women taking the pill that there exists an endogenous rhythm of well being that is coupled to, but not caused by cyclical hormones. This knowledge may help us to understand better the phenomenology of the 'normal' cycle. The role of social factors in the expression of cycle-related change is just as poorly understood as the complex influence of biological factors. Thus a third portion of this thesis is devoted to exploring the nature of women's beliefs about their cycles, and investigating how they may 'translate' in their experience and reporting.

The first study aimed to relate the degree of residual ovarian function during pill cycles to subjective state. Two pill types that deliver the same synthetic hormones, but in different dose regimens, were compared. Volunteers were monitored for ten weeks with daily twenty-one item, uni-polar visual analogue symptom diaries and daily early morning urine samples. The primary urinary metabolites of oestrogen and progesterone were measured in the urine using ELISA techniques. Diary and hormone results were then subjected to a variety of statistical analyses which revealed that all women showed

a small degree of ovarian recovery which did not differ according to pill type, and only related to the severity of certain, physical, symptoms.

This sample of women also took part in an in-depth semi-structured interview of contraceptive, menstrual and other reproductive attitudes. The content of these interviews was incorporated into a questionnaire on menstrual health and reproductive attitudes that was administered to over one thousand consecutive family planning clinic attenders. Analysis of a random sample of five hundred of the completed questionnaires showed that while women taking the pill differ from other contraceptive method users on a number of demographic variables and those questions relating to features of their method, they generally do not differ on attitudes to vaginal bleeding and the cycle.

This questionnaire served as a recruitment device for the final study reported in the thesis. Evidence from this thesis and the previous research literature indicates that cyclical change in subjective state during pill taking cannot be fully accounted for by levels of endogenous or exogenous steroids. The combined pill cycle was used as a model in which to test the hypothesis that the variation in well being which some women experience over their cycle has in-built momentum, independent of the steroid hormones. In a double-blind controlled study established pill takers were given two conventional four-week cycles of low dose combined pills followed by four months of pills in one of three temporal regimens. One group had four-week control cycles throughout, another group had four months of active pills continuously, and the third group had one cycle extended with two extra weeks of active pills. Volunteers completed daily, sixteen-item, ordinal scale symptom diaries and collected early morning urine samples three times a week.

There was evidence in the diary data of continued circa-monthly oscillation in mood and physical well being in the two groups that experienced extended pill taking. There was no consistent relationship between subjective state and the patterns of urinary oestrogen or vaginal bleeding over time. The results of this exploratory study suggest that there may be an endogenous pattern of subjective state that is entrained by the hormonal cycle. Perhaps this will be a more fruitful area for future research into the aetiology of cycle-related change in well being, than further studies of direct hormonal causes.

Abbreviations and Key Words

Abbreviations

ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BTB	Breakthrough bleeding; refers to any bleeding which occurs on active pills
C.V.	Co-efficient of variation
CASH	Cancer and Steroid Hormones Study; large scale epidemiological survey, USA
CEE	Conjugated equine oestrogen
CL	Corpus luteum
CNS	Central nervous system
CRT.	Creatinine
DSG	Desogestrel
E	Extroversion scale of the Eysenck Personality Inventory
E-3-G	Oestrone-3α-glucuronide
E_2	Oestradiol 17ß
EDA	Ethynodiol diacetate
EE	Ethinyloestradiol
ELISA	Enzyme linked immunosorbent assay
EMU	Early Morning Urine sample
EPI	Eysenck Personality Inventory
FDA	Food and Drug Administration, USA
FPC	Family Planning Clinic
FSH	Follicle stimulating hormone
GNRH	Gonadotrophin releasing hormone
GnRH-a	Gonadotrophin releasing hormone agonist
GSD	Gestodene
H-P-O	Hypotholamic-Pituitary-Ovarian axis
hCG	Human chorionic gonadotrophin
HRT	Hormone replacement therapy
IUCD	Intrauterine contraceptive device
LH	Luteinizing hormone
LLDD	Late luteal phase dysphoric disorder
LNG	Levonorgestrel

LYN	Lynestrenol
MANOVA	Multivariate Analysis of Variance
MAO	Monoamine oxidase
MDQ	Moos Menstrual Distress Questionnaire
MES	Mestranol
MHLCS	Multidimensional Health Locus of Control Scale
MHQ	Menstrual Health Questionnaire, upon which the MHRAQ was based
MHRAQ	Menstrual Health and Reproductive Attitudes Questionnaire, three versions
MMPI	Minnesotta Multiphasic Personality Inventory
MPA	Medroxyprogesterone acetate
N	Neuroticism scale of the Eysenck Personality Inventory
NEA	Norethisterone acetate
NET	Norethisterone
NIMH	National Institutes of Mental Health
NOR	Norethynodrel
NRG	Norgestrel
OC	Oral contraceptive; refers to low dose combined preparations unless otherwise stated
OxFPA	Oxford Family Planning Association; ongoing epidemiological study
P-3-G	Pregnanediol-3α-glucuronide
P_4	Progesterone
PAF	Premenstrual Assessment Form
PCA	Principle Components Analysis
PFI	Pill free interval; usually refers to seven pill free days between pill packets
PMS	Premenstrual Syndrome
PRC	Phase response curve
QC	Quality control sample
RCGP	Royal College of General Practitioners; large scale epidemiological survey
REL	Reproductive Endocrinology Laboratories, Edinburgh
REM	Rapid eye movement sleep
RIA	Radioimmunoassay
RU486	Synthetic anti-progestagen compound
SAD	Seasonal Affective Disorder
SCN	Suprachiasmatic nuclei
SES	Socio-economic status

TSA	Time series analysis
USS	Ultrasound scanning, abdominal scanning of the ovaries
VAS	Visual analogue scales
WHO	World Health Organization

Key Words and Special Usages

Bleed/s Refers to vaginal bleeding while taking OCs. As this is hormone withdrawal bleeding, to refer to it as a "period" or "menstruation" is incorrect and misleading.

Endogenous Refers to hormonal secretions or biological rhythms which are spontaneous and inherent to the woman.

Equipment Refers to the items used to collect vaginal blood, namely tampons and pads. Used in preference to value laden terms such as "*sanitary* towels".

Exogenous Refers to hormones or biological rhythms which are introduced or controlled from the external environment of the woman.

Subjective state Refers to self-reported emotional and physical state.

Symptom/s The term symptom is used throughout this thesis to refer to the changes in state/well being which vary in relation to the hormonal cycle. This term is problematic because it implies a disease state. Unfortunately there is no obvious alternative, therefore it is used in a generic way with the caveat that it is not intended to reinforce an illness model of women's cycle-related experience.

Volunteers This term has been used in preference to "subjects" which implies passivity and objectification. The women who took part in this research were conscious participants in the research process, and generously gave up their time as volunteers.

Well being Refers to both emotional and physical state.

Zeitgeber Refers to any force in the internal or external environment of the individual which acts as a timekeeper or timegiver in a rhythmic biological process.

Chapter 1 Introduction

Societies are built around systems of classification. One of the most basic classifications is the distinction made by biological sex, or gender. This division into female and male is made on the basis of dimorphism in reproductive physiology. There are obvious biological differences. Heaped on top of these and wedded to them are a whole host of different patterns of social behaviour, training, and expectation. This nature-nurture interaction makes it extremely difficult to establish what are genuine biologically determined differences between the sexes. One of the most conspicuous outward differences, apart from the obvious secondary sexual characteristics, is that women have menstrual cycles. Given the bold division between male and non-male, it is not surprising that a good deal of biological and social significance is attached to the menstrual cycle, to its functional and its symbolic meanings. A primary focus of menstruation-related scientific discourse, both ancient and modern, is the nature, meaning, and function of the sensory concomitants of the female reproductive cycle.

The more this phenomenon is researched the more it is evident that there is no simple, mechanistic relationship between the gross biological features of the steroid cycle and women's experience of changes in well being over the menstrual cycle. However, it is certain that there is a marked temporal relationship between the cycle and changes in well being for a proportion of women. Classically negative moods and uncomfortable physical sensations are observed to occur before or during menstrual bleeding. These are pronounced in some women, and the majority of women detect some minor change in mood or physical state that alerts them to impending menstruation. A greater understanding of the mechanisms which cause such variation is of theoretical interest, sociological importance, and clinical significance. The purpose of this research project has been to explore a number of different, but possibly interrelated, aetiological mechanisms for cycle-related variation in mood and physical state.

The starting point of these investigations is the fact that many women who experience cycle-related changes continued to do so to a similar extent when using combined oral contraceptives, although the pill cycle is physiologically distinct from the menstrual cycle. The research comprises two experimental investigations, one questionnaire survey, and a series of clinical case studies. Three causal factors are considered progressively in this thesis with women using oral contraception, including: 1) the role of persistent low level ovarian function during pill cycles, 2) the nature of the belief

Chapter 2 Cyclical Change in Well Being: Characteristics and Possible Aetiologies in the Oral Contraceptive Pill and Menstrual Cycles

The research reported in this thesis bridges a number of different disciplines in social and biological science including the menstrual and oral contraceptive pill cycles and their sequelae, notably cycle-related changes in well being and attitudes, and biological rhythms. Each of these areas has a large research literature of its own, therefore the review that follows covers selected material that is of direct theoretical, methodological, or empirical relevance to the investigations described in this dissertation.

2.1 The Comparative Neuroendocrinology of the Menstrual and Oral Contraceptive Pill Cycles

The human ovarian/menstrual cycle is a continuous, rhythmic developmental process. It arises from the coordinated functioning of the ovaries and the central nervous system. The endpoints of the interplay between these systems are the functional capacity to reproduce offspring, and menstrual bleeding when pregnancy does not ensue. A brief description of the complex sequence of endocrine events and morphological changes which comprise the "normal menstrual cycle" is necessary background to the questions addressed by this thesis. In particular, one must appreciate the key events of the normal menstrual cycle in order to understand the mode of action of oral contraceptive steroids, and how the combined pill cycle differs physiologically from the ovarian cycle. This section has been placed at the beginning of this chapter because the very existence of the menstrual cycle is prerequisite for *cycle-related* change in well being, however, is not meant in any way to imply that neuroendocrine cycles are necessarily causal.

2.1.1 The "Normal Menstrual Cycle"

2.1.1.1 Steroid independent follicular growth

The growth and development of the oocyte containing follicles of the ovaries are primarily responsible for the timing of the menstrual cycle. In effect the endocrine structures in the brain and the ovary function in parallel, but modulate the activity of one another via the chemical signals which they emit (Johnson & Everitt, 1988). From puberty until the menopause the primordial follicles progress through a sequence of

spontaneous growth phases, the first stage of which is hormone independent. Each day a few primary follicles begin to grow from the state in which they have been arrested since birth, into preantral follicles. Once they reach the advanced preantral phase they have the capacity to respond to the trophic effects of brain hormones and mature further (Johnson & Everitt, 1988; O'Roirdon, Malan & Gould, 1982).

If the correct endocrine environment does not coincide with their growth pattern these follicles undergo atresia and die (Johnson & Everitt, 1988). For every one follicle which reaches ovulation, an estimated 20 others degenerate (Baker, 1982). Evidence for the fact that the ovary 'keeps time' in this hormone independent fashion comes from the fact that follicular atresia continues in women using combined oral contraception to inhibit ovulation, and therefore they experience the menopause at the same time as women in whom ovulation is not interrupted (Batzer, 1984).

2.1.1.2 Central nervous system involvement in the menstrual cycle

If a follicle is to advance into the antral phase then an exchange of information must take place between the ovary and the central nervous system via the hypothalamic-pituitary-ovarian axis. The hypothalamus is a small, but highly complex area at the base of the brain which surrounds the cerebro-spinal fluid filled third ventricle. It regulates sexual and ingestive behaviour, body temperature, and integrates autonomic activity. Each of these functions is controlled by a specific aggregate of neurones known as the hypothalamic nuclei. The regions involved with reproduction include the suprachiasmatic, paraventricular, arcuate, ventromedial, and supraoptic nuclei. The hypothalamus has neuronal links with many other regulatory centres of the brain. It has axonal projections into the posterior pituitary and median eminence, for example, and information about light input into the retina is conveyed directly through neural connections with the suprachiasmatic nuclei. The hypothalamus is therefore susceptible to sensory cues from the external environment, and is also responsive to variations in the internal endocrine and nervous system environment (Johnson & Everitt, 1988; Karsch, 1984).

The other principle neuroendocrine organ involved in reproduction is the pituitary. The pituitary, also known as the hypophysis, is situated beneath the hypothalamus in the fossa of the sphenoid bone (Johnson & Everitt, 1988). It is comprised of three functionally differentiated lobes: the anterior, intermediate, and posterior lobes. These are functionally and anatomically connected to the hypothalamus by neural and vascular

links. The hypothalamus projects specialized hormone releasing neurones directly into the posterior pituitary, which secretes oxytocin and vasopressin. The anterior pituitary is primarily involved in coordinating the endocrine events of the menstrual cycle. It is not neurally linked to the brain, but exchanges chemical information with the hypothalamus via the hypothalamo-hypophyseal portal system. A variety of different cell types are located here which correspond to specific hormones, viz. prolactin, growth hormone, ACTH, and TSH. The "gonadatrophs" are not fully specialized, but have the capacity to synthesize and secrete either luteinizing hormone (LH) or follicle stimulating hormone (FSH): the gonadotrophins (Johnson & Everitt, 1988; Karsch, 1984). These two substances are integral to the cycle and are under the stimulatory control of the hypothalamic releasing hormones: gonadotrophin releasing hormone (GnRH).

2.1.1.3 The trophic and steroid hormones

GnRH is released in a pulsatile fashion from the hypothalamus into the portal system and acts on the gonadotrophs. Pulsatility is essential for function, and GnRH released continuously in an experimental situation does not produce functional pulsatile LH or FSH secretion (Karsch, 1984). The late preantral ovarian follicle has receptors for LH and FSH, and if binding occurs the follicle proceeds into the antral phase, becoming a Graffian follicle. The gonadotrophins promote the secretion of steroid hormones within the cells of the developing follicle. The two main steroid hormones produced by the ovary are the oestrogens, predominantly oestradiol-17ß (E_2), and progesterone (P_4). The precursors in the biosynthesis of oestradiol are the androgens-androstenedione and testosterone. There are two different cell types in the developing follicle which are selectively responsive to gonadotrophins: the thecal cells which under the influence of LH promote androgen secretion, and the granulosa cells which convert, or aromatize, testosterone to E_2 in response to FSH. Progesterone is secreted by the structure which arises from the follicle after ovulation, the corpus luteum (CL) (Johnson & Everitt, 1988; Baird, 1984). The ovary produces a number of other non-steroidal substances which have hormone-like actions such as prostaglandins, relaxin, oxytocin, and inhibin. These will not be discussed further here.

2.1.1.4 The timing of the endocrine events of the cycle

Figure 2.01 is a schematic drawing showing the levels of the steroids and gonadotrophins over the normal menstrual cycle. Being a genuine cycle, the menstrual cycle has no particular starting point or end, however, the convention is to consider the

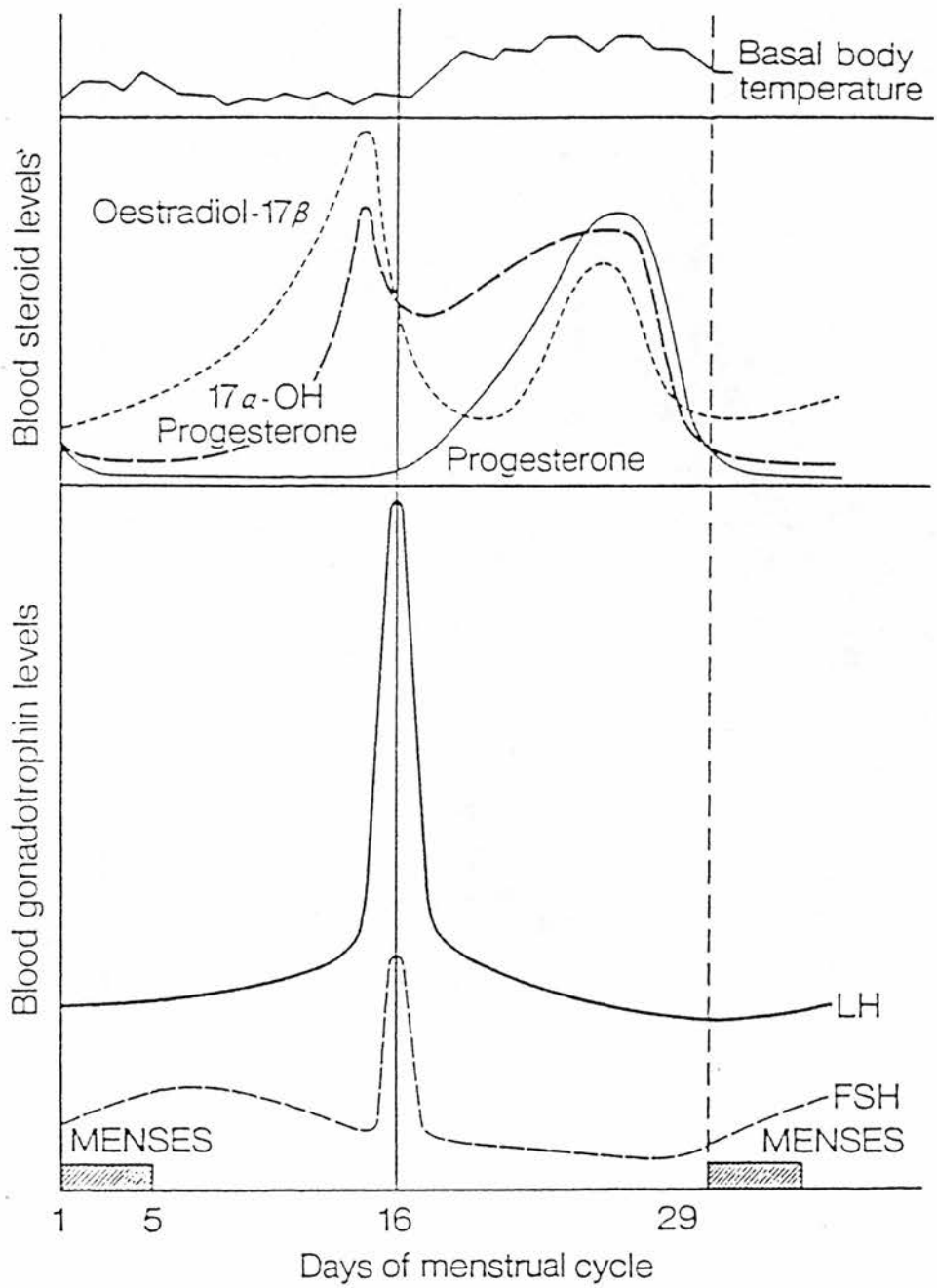

Figure 2.01 Schematic graph of steroid and gonadotrophin levels during the normal human menstrual cycle from Short (1972), p.66.

first day of menstrual bleeding as day one of the cycle (Vollman, 1977). At day one of the cycle E_2 and P_4 levels are at their lowest. Pulses of LH and FSH act on the preantral follicles in the manner described above, and FSH in particular, as its name suggests, promotes the growth and differentiation of the follicles (Baird, 1984). As the follicle grows it produces increasing amounts of E_2 relative to its size. In the first half of the follicular phase of the cycle, gonadotrophin levels remain fairly constant, but in the second half of this phase E_2 from the growing follicles exerts negative feedback on the release of gonadotrophins. Oestrogen acts directly on the hypothalamus to decrease GnRH secretion, and also alters pituitary sensitivity to GnRH, thereby preventing further FSH or LH release.

Without the stimulation of FSH to grow, all the follicles but one become atretic. This follicle, known as the dominant follicle, continues to grow at an exponential rate. It produces about 90% of ovarian oestrogen during the preovulatory period (Baird, 1970; Baird & Guevara, 1969). At day one of the cycle the follicle destined for ovulation is probably only about 2mm in diameter, but by the time it ovulates it will be in the region of 25mm in size (Baird, 1984; Baker, 1982). Only the dominant follicle grows to more than about 15mm in diameter (Bomsel-Helmreich, 1985). The process by which the dominant follicle is recruited from amongst a cohort of follicles is ill understood at present (Bomsel-Helmreich, 1985; Hodgen, 1982).

Oestrogen reaches its highest level just before mid-cycle. At this time the previously negative feedback effect of E_2 on gonadotrophin release changes to positive feedback, and LH is induced to surge and FSH to rise. Thus the ovary seems to signal the brain of its preparedness for ovulation. The gonadotrophins play an important role in the final pre-ovulatory maturation of the follicle and egg via the absolute level of the LH surge, and the LH to FSH ratio. Peak E_2 precedes the LH surge by approximately 24 hours, and follicular rupture and ovulation follow after about 36 further hours (Baker, 1982).

After ovulation P_4 levels rise sharply. The most important effect of P_4 in the feedback relations of the cycle is that in the high concentrations which are seen after ovulation, it enhances the negative feedback effects of E_2 on the release of LH and FSH. Further, it prevents oestrogen from exerting positive feedback (Johnson & Everitt, 1988). Progesterone is secreted from the corpus luteum which develops out of the ruptured and involuted dominant follicle. The CL is responsible for maintaining the

endometrium and embryo during early pregnancy. P_4 levels peak approximately eight days after the LH surge and remain high for the rest of the menstrual cycle, i.e. throughout the luteal phase. Oestrogen levels during the luteal phase are almost as high as they are during the follicular phase, however, the effects of oestrogen are altered in the presence of progesterone (Johnson & Everitt, 1988).

Without fertilization and implantation the lifespan of the CL is finite, and is usually considered to be constant at about 14±3 days (Landgren, 1989; Lenton, Landgren & Sextom, 1984). Thus, variations in the length of the human menstrual cycle are generally attributable to variations in the length of the follicular, and not the luteal phase. At the end of the luteal phase the CL regresses, or undergoes luteolysis, and there is a precipitous drop in the levels of both E_2 and P_4. The hypothalamus and pituitary are thus relieved of the negative feedback control of the steroids and resume pulsatile release of GnRH, LH and FSH, and another cycle commences. The other important consequence of falling steroid levels is the onset of vaginal bleeding, the characteristics of which will be discussed below.

2.1.1.5 Effects of ovarian steroids on target tissues

The steroid hormones also influence the tissues of the uterus, cervix, vagina, fallopian tube, and breast amongst others. This thesis is primarily concerned with cyclical changes related to the steroid cycle, and thus the effects of oestrogen and progesterone on the uterus and breast are of principle interest. The follicular phase of the cycle is also known as the proliferative phase because of the effects which the oestrogens have on the uterine endometrium. E_2 causes an increase in contractility and excitability of the uterine myometrium and produces an increase in the size and number of stromal cells in the endometrium, with a consequent increase in intra-uterine surface area. E_2 acts by binding to the abundant oestrogen receptors and is also responsible for inducing the development of intracellular progesterone receptors. An endometrium which is not primed by oestrogen is not able to respond to the presence of progesterone. P_4 stimulates the synthesis of secretory material by the glands, accelerates stromal proliferation, and encourages cell enlargement. Myometrial contractility is reduced but its size increases. The progestagenic phase is also known as the secretory phase (Johnson & Everitt, 1988; Baird, 1984).

The effects of steroids on breast tissue are not well understood. However, it is known that breast changes do not parallel endometrial changes. The small units of resting

breast tissue which develop into the secretory units are called lobules. The tissue constantly undergoes concurrent waves of cell growth (mitosis) and cell death (apotosis) which are out of phase with the endometrium. The peak in cell division occurs late in the cycle during the progestagenic rather than oestrogenic phase. Many different substances act on the breast and it is possible that rather than exerting a direct effect the endocrine stimuli precipitate paracrine or autocrine regulatory systems. (Anderson, 1989, 1988).

The steroids affect many other body tissues. Oestrogens have a general influence on the cardiovascular system and metabolism, being generally protective against cardiovascular accident. Progesterone on the other hand may increase appetite, and raises body temperature via a direct influence on the hypothalamus. It may also produce sodium retention by stimulating angiotensinogen production (Johnson & Everitt, 1988). P_4 also has sedative and anticonvulsant effects (McCauley, Lan& Gee, 1992; Backstrom, Baird, Bancroft, Bixo, Hammarback, Sanders & Zelterlund, 1983a; Silbergeld, Brast & Noble, 1971).

2.1.2 The "Normal Pill Cycle"

This section is concerned with the levels of endogenous steroids and gonadotrophins which are observed during the conventional combined oral contraceptive (OC) pill cycle. Before considering the endocrinology of the pill cycle it is important to briefly summarize the history of steroidal contraception, and to chart the development of new contraceptive formulations up to those currently in widespread use. Here and throughout this thesis the emphasis will be placed on low dose combined preparations. The oral contraceptive pills are probably amongst the most researched substances in human history (Weijers, 1984). In the short lifetime of OCs an absolutely vast literature has accrued on their contraceptive and non-contraceptive effects. They have been the subject of several large, longitudinal, epidemiological investigations including those undertaken by the Oxford Family Planning Association (OxFPA), and Royal College of General Practitioners (RCGP) in this country, and the Harvard Nurses Study, and Cancer and Steroid Hormone (CASH) studies in the United States. Thus, the review of the literature contained herein will necessarily be highly selective.

2.1.2.1 The history of the combined "Pill" and formulations in current use

The term "the pill" to refer to a wonder contraceptive was originally coined by Aldous Huxley, in The Brave New World Revisited which was published in 1958, just two years before OCs became a reality (Djerassi, 1981). After working for seven years deriving synthetic steroids from the soap-like substances contained in the Mexican yam, *Diosgenin*, Djerassi and his co-workers at Syntex (from **synt**hesis and **Mex**ico) synthesized the first orally active synthetic progestagen, norethisterone[1], in 1951. This substance was submitted to Gregory Pincus and John Rock who tested its ovulation inhibiting effects, along with about 200 other substances in 1953 and 1954. Norethisterone was effective, as was norethynodrel which was synthesized by Pincus' own company, Searle, in 1952. Norethynodrel was chosen as the gestagen to use in the field trials of the first OC (Djerassi, 1981; Mears, 1966). These trials which took place in Puerto Rico in 1956 were conducted by Edris Rice-Wray, one of the few women involved in the early development of the pill (Greenblatt, 1980; Drill, 1966).

In 1957 the United States Food and Drug Administration (FDA) gave approval for the two original progestagens to be used for the treatment of menstrual disorders and infertility. By late 1959 the first combined oral contraceptive, called Enovid, was introduced, containing 0.15mg of mestranol and 9.85mg of norethynodrel (Djerassi, 1981; Greenblatt, 1980). Two years later the norethisterone containing pill, Otho-Novim was marketed. Oestrogen was only included in the first pills by accident, as a contaminant in the progestagen. It was removed, but the gestagens no longer exerted such good control over cyclical vaginal bleeding, and it was re-introduced in a controlled fashion (Djerassi, 1981).

The original pill regime involved giving oestrogen and progestagen from day five until day 24 of the cycle, i.e. for 20 days, and then allowing one week free of pills in which bleeding was to occur. The two stated objectives of this regimen were: 1) the inhibition of ovulation, and 2) the provision of regular cyclical menstruation (Mears, 1966). In the history of combined OCs only two synthetic oestrogens have been used, but a wide variety of synthetic progestagens. The original oestrogen, mestranol (MES), is the 3-methyl-ether of the second, ethinyloestradiol (EE). MES is demethylated *in vivo* in order to enable it to bind to the oestrogen receptor. EE, because it does not need to be

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[1] Norethisterone is known as norethindrone in North America.

demethylated, is more potent than MES. It acts more quickly and can be used at lower doses (Batzer, 1984; Greenblatt, 1980; Mears, 1966). All modern low dose pills contain EE; MES is rarely used (Guillebaud, 1984).

Approximately nine different progestagens have been developed and used in pills since the late 1950s. All synthetic gestagens are derived from one of two substrates: 17α-hydroxyprogesterone or 19-nortestosterone (Runnebaum & Rabe, 1987; Mears, 1966). The progestagens in the 17α-hydroxyprogesterone class are potently progestagenic, and not at all oestrogenic. They provide poor cycle control and are not very good at inhibiting ovulation (Mears, 1966) so are not used in OCs. All synthetic gestagens are based on slight manipulations of the basic, three 6-membered ring and one 5-membered ring, structure of the steroid molecule (Djerassi, 1981). The 19-nor-steroids have all been created by altering the testosterone molecule, namely deleting the carbon from position 19 (Batzer, 1984). There are three ways of classifying progestagens, according to chemical structure, biological properties, or affinity for hormone receptors. However, it is not possible to predict receptor affinity and biological properties from chemical structure in any consistent way. For example, norethisterone and norethynodrel differ by only one double bond, yet norethisterone is mildly androgenic, and norethynodrel not at all (Rozenbaum, 1982) in spite of the fact that norethynodrel is metabolized to norethisterone in the gastrointestinal tract (Djerassi, 1981). Prediction is further complicated by the fact that progestagen action depends on synergism with EE (Runnebaum & Rabe, 1987).

The 19-nortestosterone derived compounds may possess progestin-like action which delays vaginal bleeding, and causes endometrial decidualization. They may be androgen-like and promote acne and hirsuitism. Or they may behave like oestrogen (Batzer, 1984). Table 2.01 lists the various substances and their biological activities. Over the years there has been a consistent effort to reduce the dosage of both synthetic hormones in the combined pill in order to reduce adverse non-contraceptive effects (Briggs & Briggs, 1976). In this connection, the progestagens have been continually refined to improve their potency and specificity. One speaks of first, second and third "generation" gestagens (see Table 2.01). Most of the low dose pills currently in widespread use in the U.K. contain second or third generation gestagens[2], notably the

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Although the combined pill was developed in the Americas, none of the newest gestagens are in use in the United States (Djerassi, 1981). This is probably due to a variety of factors, not the least of which is the extremely rigid FDA requirements for

gonanes, which are biologically more effective than their predecessors, the estranes, and include levonorgestrel (LNG), desogestrel (DSG), and gestodene (GSD) (Runnebaum & Rabe, 1987).

Table 2.01 The 19-Nortestosterone Progestational Compounds Contained in Combined Oral Contraceptives

Trade Name	Generation	Biological Properties
Norethisterone (NET)	1st	Mildly androgenic & possibly oestrogenic
Norethisterone acetate (NEA)	1st	Mildly androgenic & possibly oestrogenic
Ethynodiol diacetate (EDA)	1st	Oestrogenic
Norethynodrel (NOR)	1st	Oestrogenic & not at all androgenic
Lynestrenol (LYN)	1st	Oestrogenic
Norgestrel (NRG)	2nd	Potently progestagenic, most androgenic & anti-oestrogenic
Levonorgestrel (LNG)	2nd	Progestagenic, weakly androgenic, anti-oestrogenic, but not oestrogenic or anti-androgenic
Desogestrel (DSG)	3rd	Progestagenic, strongly anti-oestrogenic, but not anti-androgenic
Gestodene (GSD)	3rd	Most progestagenic, but not oestrogenic

(Information from Runnebaum & Rabe, 1987; Batzer, 1984; Guillebaud, 1984; Rozenbaum, 1982; Djerassi, 1981; Greenblatt, 1980; Mears, 1966)

Table 2.02 lists the trade names and components of all the low dose combined oestrogen-progestin pills currently in use in the U.K.. There have been four stages in the development of the combined pill. First there were the original high dose oestrogen, high dose progestagens formulations, which were followed by "sequential"

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drug safety testing (Smith, Potts & Fortney, 1991), including the obstructive practice whereby the results of clinical trials carried out outside the United States are not allowed as evidence, and must be repeated in American samples (David Hollingworth, 1990, personal communication).

pills which administered oestrogen alone for the first half to two-thirds of the cycle and then administered about a week of oestrogen plus progestin. In the third stage, pills began to appear which contained a constant low dose of both steroids, and most recently various "phased" preparations have been developed, which provide staged dosages of one or both hormones over the cycle (Batzer, 1984). All modern low dose pills contain between 20 and 40µg of EE, and one of six different gestagens. There are nine different monophasic preparations and four phased ones (see Table 2.02).

Table 2.02 Low Dose Combined OCs Currently Marketed in the U.K.

Monophasic Pill Name	Steroid Constituents	Regimen
Norimin / Neocon 1/35	EE 35µg + NET 1000µg	21 days
Brevinor / Ovysmen	EE 35µg + NET 500µg	21 days
Conova 30	EE 30µg + EDA 2000µg	21 days
Loestrin 30	EE 30µg + NEA 1500µg	21 days
Loestrin 20	EE 20µg + NEA 1000µg	21 days
Eugynon 30 / Ovran 30	EE 30µg + LNG 250µg	21 days
Microgynon 30 / Ovranette	EE 30µg + LNG 150µg	21 days
Marvelon	EE 30µg + DSG 150µg	21 days
Mercilon	EE 20µg + DSG 150µg	21 days
Minulet / Femodene	EE 30µg + GSD 75µg	21 days
Phasic Pill Name	**Steroid Constituents**	**Regimen**
Binovum	EE 35µg + NET 500µg EE 35µg + NET 1000µg	7 days 14 days
Synphase	EE 35µg + NET 500µg EE 35µg + NET 1000µg EE 35µg + NET 500µg	7 days 9 days 5 days
Trinovum	EE 35µg + NET 500µg EE 35µg + NET 750µg EE 35µg + NET 1000µg	7 days 7 days 7 days
Logynon / Trinordiol	EE 30µg + LNG 50µg EE 40µg + LNG 75µg EE 30µg + LNG 125µg	5 days 6 days 10 days

Key: EE-ethinyloestradiol, NET-norethisterone, EDA-ethynodiol diacetate, NEA-norethisterone acetate, LNG-levonorgestrel, DSG-desogestrel, GSD-gestodene.

It is worth briefly considering the rationale behind the development of the phased preparations, especially the triphasics. The primary purpose for developing triphasics

was to reduce the total quantity of steroid ingested over the cycle in order to minimize metabolic changes and decrease intercycle bleeding (Greenblatt, 1980; Pasquale, 1984; Hale, 1987; Woutersz, Butler, Cohen, Korba & Canavan, 1987). Table 2.03 shows the difference in dosage between the triphasic Logynon/Trinordiol and its monophasic analogue Microgynon/Ovranette. Note that Logynon/Trinordiol is the only triphasic preparation available in which both steroids vary in dose over the cycle. Greenblatt (1980) cites that increased understanding of the differential action of the various gestagens was instrumental in efforts to refine their use and in particular, to generate the most favourable oestrogen-progestagen ratio. Clinical trials of the three different triphasic formulations show that the reduction in steroid dose has resulted in fewer alterations in metabolic pathways, lipid chemistry, coagulation profiles, and blood pressure (Hale, 1987).

Table 2.03 Comparative Dosage of Steroids in a Monophasic versus a Triphasic Preparation

Brand of OC	Made by	Total EE per cycle	Total LNG per cycle	Mean EE per day	Mean LNG per day
Microgynon	Schering	630 µg	3150 µg	30 µg	150 µg
Ovranette	Wyeth	630 µg	3150 µg	30 µg	150 µg
Logynon	Schering	680 µg	1925 µg	32.4 µg	91.7 µg
Trinordiol	Wyeth	680 µg	1925 µg	32.4 µg	91.7 µg

Legend- Ethinyloestradiol (EE), Levonorgestrel (LNG).

Hale (1987) notes that "incidental side effects, such as acne, depression, and nausea are also reduced" while the regime is beneficial because it "emulates the normal menstrual cycle" (p1058). It is questionable whether or not there is any material benefit to women in having a pill cycle that mimics the menstrual cycle. But possible improvements in metabolic parameters and well being may be important in studies of the relationship between steroid production and cyclical change.

2.1.2.2 Mode of action and ancillary effects of combined OCs

The main target organs of the steroids in the combined pill are the pituitary and the uterus (Runnebaum & Rabe, 1987; Gilmer, 1987). OCs reduce the release of LH and FSH from the anterior pituitary and most importantly block the LH surge (Runnebaum & Rabe, 1987; Loudon, 1985; Batzer, 1984; Greenblatt, 1980; Drill, 1966; Mears, 1966) thereby preventing ovulation. In the early days of pill development they did not

believe that synthetic steroids had any direct action on the hypothalamic GnRH pulse generator (eg-Mears, 1966), however, it is now thought that the pill does influence GnRH release through complex interaction with endogenous opioid peptides (endorphins), oestrogens, and CNS neurotransmitters (Batzer, 1984; Greenblatt, 1980). Both steroids in the combined pill act on the CNS. EE has a negative feedback effect on LH and FSH, as does oestradiol, and it also attenuates the CNS suppressive effects of the progestagen (Loudon, 1985; Batzer, 1984). Early work also suggested that the pill did not affect the ovary, and that its responsiveness to gonadotrophin was not altered (Drill, 1966), however it is now understood that 19-nortestosterone derived gestagens do act directly on the ovary by impairing or suppressing luteal function (Loudon, 1985). Equally, original animal studies suggested that LH is more easily suppressed than FSH (Mears, 1966) and recent work seems to confirm this (eg. Elstein, Morris, Groom, Jenner, Scarisbrick & Cameron, 1976). Thus the pattern of ovarian follicles recruitment and maturation is disrupted by pill taking, while the hormone independent changes continue (Batzer, 1984).

OCs have multiple ancillary effects in addition to inhibiting ovulation, many of which contribute to the method's overall contraceptive efficacy. For example, tubal secretions and peristalsis are altered (Runnebaum & Rabe, 1987; Batzer, 1984) influencing egg transport, cervical mucous rapidly becomes progestagenic (Runnebaum & Rabe, 1987; Greenblatt, 1980; Mears, 1966), basal body temperature is raised, and the vaginal epithelium is altered, as is hepatic metabolism (Runnebaum & Rabe, 1987). The pill has profound effects on the uterine endometrium and the breast. OCs inhibit myometrial contractions but promote glycogen storage in the endometrium (Runnebaum & Rabe, 1987). The constant administration of both oestrogen and progestin leads to an inhibition of the proliferative process and premature secretory transformation with stromal decidualization and glandular atrophy (Pincus, 1965). The normal phase relationship of steroids in the menstrual cycle is disturbed, notably by the relative absence of oestrogen (except briefly and at low levels during the pill free interval) unopposed by progesterone which would normally prime the tissue and promote progesterone receptors. The consequence is a mixed distribution of secretory and proliferative glands throughout pill taking, and relative atrophy in the days before withdrawal bleeding (Baird & Glasier, 1991; Runnebaum & Rabe, 1987; Gilmer, 1987; Batzer, 1984; Mears, 1966). The EE in the pill "stabilizes" the endometrium (Batzer, 1984), without it, bleeding is erratic and unpredictable, as it may be on progesterone only pills (POP).

There is relatively limited information of the influence of OCs on breast tissue. Progestins stimulate the proliferation of breast lobule epithelium with greater cell proliferation seen during the would-be late proliferative and secretory phases than is seen during the normal menstrual cycle (Anderson, 1989, 1988; Gilmer, 1987). This may help to explain the breast tenderness and/or distension which many women experience during pill taking, and which has been related to the progestagen content of the pill (eg- Mears, 1966). Anderson (1989, 1988) has found that the duration of pill use and the specific gestagen is relatively unimportant in predicting breast hyperplasia on the pill, but that it is very strongly associated with youth and nulliparity, both of which are likely to be confounded with pill taking.

A wide variety of serious and so-called "minor" side effects have been reported in combined pill takers. It is not the purpose of this thesis to make a comprehensive review of these effects, however, it is important to consider the so-called "nuisance" effects as many of these are similar to the symptoms and changes which may be experienced cyclically in relation to the menstrual cycle. They include breast tenderness, weight gain, withdrawal headaches, changes in libido, acne, depression, nausea, and breakthrough bleeding. As suggested above, breast changes seem to be due to the influence of the progestagen component.

Changes in body weight are common on the pill. For example, one study comparing Marvelon and Mercilon found that between 13 and 19% of participants had gained weight at the 6th and 12th cycle of use, and 10 to 17% had lost (Tuimala, Saranen & Alapiessa, 1987). In the U.K. clinical trials of Marvelon the incidence of weight gain (about 1 lb by cycle 6) was higher, appearing in about one-third of women (Wiseman, Bowie, Cogswell, Dewsbury, Hamilton, Hutchinson, Kirkman, Loudon, Lincoln, Lyons, Pullen & Wilson, 1984). It has been suggested that there are two mechanisms by which weight gain can occur: oedema induced by oestrogenic pills, and genuine weight gain due to the "mildly anabolic" effects of some gestagens (Mears, 1966).

In some women the sudden withdrawal of steroids at the end of the 21-day pill regime precipitates a migraine type-headache. These persist with continued pill use (Mears, 1966), and can sometimes be circumvented by taking several packets of pills in a row without the usual seven day pill free interval. Libido may be increased or decreased by the pill, and some women become depressed (Mears, 1966). Androgenic, anti-

oestrogenic pills may promote acne through increased sebum production (Schering, 1989; Mears, 1966), and nausea seems to be related to high oestrogen doses (Mears, 1966). In one study a high incidence of side-effects including decreased libido, headaches, abdominal pain and bloating, dizziness, and intercycle bleeding were recorded by women who were given a placebo and told that it was an OC (Aznar-Ramos, Giner-Velázquez, Lara-Ricalde & Martínez-Manautou, 1969). The authors suggest that the side effects are psychogenic, but it is possible that these women would have experienced these changes anyway and were not falsely attributing changes to the drug. It is difficult to quantify attributions, however, they remain an important and potentially significant contributor to adverse reactions to oral contraception.

2.1.2.3 Low dose pills: At the margin of efficacy?

There is a growing body of evidence which suggests that the steroid dosage of low dose combined pills is close to the lower limit for maximum efficacy. Whereas the original high oestrogen, high progestagen pills probably overdosed women by a factor of ten- or even one-hundred fold, there may be a real risk of modern pill failure in a small proportion of women. The conventional pill regimen involves starting a new formulation on day one or day five of the menstrual cycle, and thereafter following the 21 days of active pills with a seven day pill free interval (pfi), thus creating an artificial cycle. The "week-off" is intended to permit vaginal bleeding, ostensibly to prevent endometrial atrophy, to allow metabolic parameters altered by pill steroids to "recover", and to make the regime acceptable to women who expect to bleed at regular intervals (Rutter, Knight, Vizzard, Mira & Abraham, 1988; Guillebaud, 1987).

The problem is that, at least theoretically, having seven pill free days may allow sufficient recovery of the hypothalamo-pituitary-ovarian (H-P-O) axis that folliculogenesis may have progressed to the mid-follicular phase or beyond by the time pill steroids are re-introduced. It is therefore important to quantify the extent of "residual" ovarian function for two reasons: 1) to estimate the degree of risk of escape ovulation and potential contraceptive failure, and 2) to determine whether or not continued endogenous hormone production may relate to the experience of cycle-related changes in well being.

A number of approaches have been used to try and quantify the amount of ovarian and gonadotrophin activity that occurs in pill cycles including serum and urinary assay of steroid and gonadotrophin levels, with or without the deliberate omission of pills,

GnRH challenges, and follicular visualization using abdominal ultrasound scanning. These strategies are variously concerned to discover: a) whether or not steroid levels enter the normal range of the menstrual cycle[3], b) whether rising oestrogen is accompanied by ovarian follicular growth at a potentially functional rate[4], c) whether a dominant follicle is recruited and matures sufficiently to be potentially ovulatory, d) whether LH and FSH are being released in a pulsatile fashion, and e) whether an LH surge might occur causing ovulation.

In an early study which tracked the hormones of women starting to take Microgynon only FSH rose during the pfi, but returned to baseline by the end of the first week of pills (Elstein et al., 1976). The authors conclude that FSH is the most sensitive indicator of recovery from steroid suppression but that there is no residual ovarian function on this pill. However, it seems that these conclusions were unwarranted given that only three women were studied. Another small study of new Microgynon takers found that steroids and gonadotrophins were basal with no peaks during the first month of use (Ollo, el Sokkary, Darwish, Khamis & Souka, 1990).

However, other studies with larger samples, and/or using ultrasound have shown that significant ovarian function occurs in about 10-20% of women during low dose pill cycles (Thomas & Vankrieken, 1990; van der Spuy, Sohnius, Pienaar & Schall, 1990; Hamilton & Hoogland, 1989; Killick, Eyong & Elstein, 1987; Westcombe, Ellis & Fotherby, 1987; Elstein & Killick, 1985; Molloy, Coulson, Lee & Watters, 1985; van der Vange, Bennink, Tennekes & Haspels, 1985) particularly if women were required to miss pills deliberately (Killick, 1989; Smith, Kirkman, Arce, McNeilly, Loudon & Baird, 1986; Landgren & Diczfalusy, 1984; Wang, Shi, Cekan, Landgren & Diczfalusy, 1982; Chowdhury, Joshi, Gopalkrishna, Betrabet, Mehta & Saxena, 1980; Morris, Groom, Cameron, Buckingham, Everitt & Elstein, 1979).

In the majority of women one observes a rise in endogenous oestrogen during the pill free interval which gradually returns to baseline over the first week of pill taking (Thomas & Vankrieken, 1990; van der Spuy et al., 1990; Killick et al., 1987;

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Measures of progesterone are made to detect suspected "escape ovulation".

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There is generally a fixed relationship between ovarian oestrogen output and the size of the follicles residing in the ovary at any given time. The amount of serum oestradiol in pg/ml is roughly equivalent to the sum of squares of the diameter of the follicles in millimetres divided by two (Killick, Eyong, and Elstein 1987).

Westcombe et al., 1987; Smith et al., 1986; van der Vange et al., 1985; Landgren & Diczfalusy, 1984; Wang et al., 1982; Chowdhuury et al., 1980). LH and FSH release recover to pre-pill levels very quickly over the pfi, with absolute levels, and the pulsatile pattern of release restored to an early follicular phase pattern by the seventh pill free day (van der Spuy et al., 1990; Cohen & Katz, 1979). LH and FSH rise after an intravenous challenge with GnRH, suggesting near normal H-P-O responsiveness (Cohen & Katz, 1979; Rubinstein, Moguilevsky & Leiderman, 1978) and that ovulation can occur, especially if pills are missed around the pfi (eg. Killick, 1989). Progesterone remains basal unless ovulation occurs. Two studies have reported ovulation rates of just under 5% in women using the formulation Logynon/Trinordiol (Westcombe et al., 1987; van der Vange et al., 1985).

The amount of follicular growth seen in ultrasound scans varies from one study to the next. All women seem to have some follicular growth during the pfi, and in about half there are multiple follicles of which one is at least 7mm in diameter (Hamilton & Hoogland, 1989; Molloy et al., 1985). Dominant follicles of between about 15mm and 30mm have been observed in between 5% and 23% of cycles (Hamilton & Hoogland, 1989; Killick et al., 1987; van der Vange et al., 1985). However, it is unlikely that many of these are capable of fertilization or implantation if they do ovulate since their growth rate is retarded relative to that of normally cycling controls (Killick et al., 1987). This may explain the discrepancy between the incidence of large follicles seen on scans and luteal phase progesterone levels. Several studies have shown a lack of concordance between steroid levels and follicular size at scanning (Thomas & Vankrieken, 1990; Elstein & Killick, 1985). This highlights the fact that, if possible, hormone assay should be accompanied by morphological measurement.

The tendency to experience continued ovarian function seems to be specific to certain individuals (eg. Westcombe et al., 1987; Landgren & Diczfalusy, 1984), and to persist over time with continued pill use (Thomas & Vankrieken, 1990; Molloy et al., 1985; van der Vange et al., 1985; Wang et al., 1982). It has been suggested that some sort of adaptation through habituation may occur in long established pill users which accounts for persistent ovarian function (Landgren & Diczfalusy, 1984). There has been particular concern that the very low doses of steroid contained in triphasic pills might permit ovulation to occur in some women, and the failure rate of these pills is marginally higher than monophasics with similar constituents (Fay, 1982; Graham, 1982).

Though many studies have focused on triphasic pills for this reason, the evidence for a difference in the degree of residual ovarian function between monophasic and triphasic pills is equivocal. Molloy et al. (1985) did not find greater follicular size in triphasic takers, however Smith et al. (1986) did find higher E_2 levels in Trinordiol users than Microgynon users in the first two weeks of pill administration. Overall it appears that ovarian recovery occurs as a function of the seven day pfi, and that maximal endogenous oestrogen production is seen at the end of the pfi or in the early days of subsequent pill taking but that ovulation is unusual. There is evidence of considerable inter-individual variation in the degree of ovarian recovery, and it is uncertain whether or not different pill formulations permit variable degrees of H-P-O responsiveness.

2.2 Patterns of Vaginal Bleeding

One of the most important features which distinguishes woman's reproductive cycle and that of other Old World primates, from the oestrous cycle of other mammals is cyclical vaginal bleeding: menstruation. The word menses is the plural of the latin word *mensis* for month, which in turn comes from the word for the moon and is related to latin words for measurement, in this case, of time (Shuttle & Redgrove, 1986). The length of the menstrual cycle has historically been related to the length of the lunar cycle, or the synodic month, which has a mean of 29.53 solar days (Shuttle & Redgrove, 1986; Vollman, 1977). Some of the earliest consistent records of menstrual cycle length, such as that of Clos in the nineteenth century, have sought to relate the timing of bleeding to particular phases of the lunar cycle (Vollman, 1977). (The evidence for the manner in which the moon may indeed relate to menstrual cycle experience will be considered in the section on environmental influences below.)

This section is concerned with describing the mechanism of menstruation and its characteristics across women, notably the parameters of bleed volume and duration, as well as the length of the "normal" menstrual cycle. After establishing the background of the menstrual cycle, the features of bleeding during the OC cycle will be considered.

2.2.1 Bleeding During the Menstrual Cycle

2.2.1.1 The physiology of menstrual bleeding

In most mammals the thick secretory endometrium which develops under the influence of oestrogen and progesterone over the cycle is reabsorbed if fertilization does not take place. Those Old World primates, however, which possess specialized coiled arteries and arterioles in the endometrium known as spiral arterioles experience spontaneous uterine bleeding after the fall of steroids at the end of the cycle (Abel, 1985; Shaw & Roche, 1980). The precise mechanism responsible for the onset of bleeding is not fully understood. In a series of classic experiments carried out in the 1930s, Markee transplanted endometrial tissue to the eye in 41 rhesus monkeys, and observed the cyclical changes in the tissue which accompanied uterine changes over 432 menstrual cycles (see Shaw & Roche, 1980). The endocrinology and bleeding pattern of the rhesus monkey is more comparable to that of women than any other primate species.

Observation of the endometrial transplants under the microscope in conscious animals during the late luteal phase revealed vasodilation and cellular oedema. Then prior to bleeding, there was a reabsorption of fluid from the stroma and tissue shrinkage of about 60%. This caused intense constriction of the arteries and spiral arterioles between 4 and 24 hours before the onset of bleeding resulting in ischaemia and hypoxia, followed by necrosis, venous dilation, and leukocyte infiltration. The extent of endometrial shedding was reported to be proportional to the duration of intense vasoconstriction. Markee proposed that the majority of menstrual blood derived from short spurts from the arteries while venous bleeding was slighter, but more prolonged (Shaw & Roche, 1980).

These changes accompany luteal regression. The ubiquitous prostaglandins peptides (Pg's) have also been implicated in the mechanism of both luteolysis and menstruation (for reviews see Smith, 1991 and Shaw & Roche, 1980 respectively). $PgF_2\alpha$ stimulates the contraction of the myometrium, and a high ratio of $PgF_2\alpha$ to PgE_2 is observed in cases of heavy bleeding. However, the actions of Pg's are thought to be contributory and not entirely causal (Smith, 1986; Abel, 1985). Hertz (1986) has suggested that an autoimmune rejection of the endometrium may occur when steroid levels are at their nadir. Blood flow reduces over the course of menstruation as the arteries reconstrict. Clotting, or the formation of vascular thrombi also seems to

contribute to haemostasis. These thrombi are then shed with the endometrium of the next menstruation (Shaw & Roche, 1980).

2.2.1.2 Menstrual cycle length

Vollman (1977) suggests that the widespread myth that the human menstrual cycle extends for 28 days from the onset of one bleed to the onset of the next is a cabala which derived from modern physicians and metaphysicists formalizing women's reckoning that the cycle is "usually about four weeks" to an actual 28 days. He and several others in the research literature have shown through careful recording of consecutive menstrual cycles over many years that rather than *une règle absolue* of a 28 day cycle, variability is the rule. In particular, Vollman and Treloar have demonstrated that menstrual cycle length parallels the dynamic, developmental process of reproductive function over the life course (Vollman, 1977; Treloar, Boynton, Behn & Brown, 1967).

Treloar et al. (1967) collected data on 2702 American women over 275,947 cycles, or 25,825 woman years of menstrual experience between 1933 and 1961. All of this information was collected before the introduction of steroidal contraception, and is therefore purely "menstrual cycle" data. The age range spanned the whole of reproductive life, and in a few cases the same woman was tracked from menarche to the menopause. The overall finding was that cycle length changes in a U-shaped fashion over the reproductive years.

During the first approximately seven years after menarche cycles tend to be longer and more variable than at mid-life. Equally, cycle length becomes increasingly variable and the duration longer, as one approaches menopause. The process is like the mirror image of menarche, but takes about one year longer on average. For example, the median cycle length in this sample, 18 months after menarche, was 33 days, and 30 days four years post-menarche. With increasing "gynaecological maturity" cycle length gradually shortens, and becomes less variable. Thus cycle length declines in a linear fashion between the ages of about 21 and 39 by about 1/10 of a day per year, reaching its lowest median length at 26 days approximately eight years before the menopause. After that there is a curvilinear increase in cycle length up to a peak of 44 days 18 months before cycling ends. The variability of cycle length also decreases in a linear fashion in the middle phase of life; for example, the median SD at 20 years is 2.75 days versus 1.83 days at 36 years (Treloar et al., 1967). A subsample of young and old age

cohorts amongst Treloar's population were investigated to clarify the endocrine basis of age related changes in cycle length. Variable bleeding frequency at the beginning and the end of reproductive life is due to changes in follicular maturation. Menarcheal girls have long cycles due to delayed follicular maturation, while in the peri-menopause cycles get shorter due to more rapid folliculogenesis, and raised gonadotrophin levels (Sherman & Korenman, 1975).

There is also evidence that young women may not ovulate in all cycles which might contribute to variable cycle length. Metcalf & Mackenzie (1980) assayed the principle urinary metabolites of the steroids, oestrone and pregnanediol, weekly for three consecutive cycles in 254 women aged 15 to 39. All volunteers were at least four years from menarche. They found that young women aged 20 to 24 (n=108) had ovulatory pregnanediol levels in only 62% of cycles, compared with 88% of 25 to 29 year olds (n=58), and 91% of women over 30 (n=44). They also found evidence for potential environmental influences on the incidence of ovulation as students and women living in flats or hostels ovulated about 30-40% less often than those living at home with relatives (see section 2.7.3.2 below).

Vollman's (1977) findings in 691 Swiss women were very similar to Treloar's. Volunteers ranged in age from 14 to 63 years Fifty-two per cent of women kept records of their cycles for ≤1year, while 48% of the women produced 91% of the data keeping up monitoring in some cases for as long as 39 years. He found that the actual and reported age of menarche ranged from 9 to 21years. During the gynaecologically mature years of mid-life variability in cycle length tended to be restricted to between 3 and 5 days. "Runs" of more than 2 or 3 successive cycles of the same length were extremely rare. Amongst 656 women over 31,645 cycle there were only 33 runs of 5 or more cycles which occurred in 32 women, producing a rate of 1.5 runs per 1000 cycles. When runs did occur they were likely to be of 27 or 28 day cycles. These data completely refute the concept of a regular 28 day menstrual cycle. Twenty-eight day menstrual cycles were modal in this population, but constituted only 12.4% of cycles, and 27 day cycles were nearly as common.

Women are often criticised for reporting that they experience very "regular" cycles when in fact they are quite variable, and are considered "unreliable", or poor at recall or prediction (eg- Snowden & Christian, 1983). In fact, women seem to use "regular" or "28 days" as a vernacular to indicate that they consider themselves to be normal in their

menstrual characteristics (Treloar et al., 1967). Although cycle length does vary across women, within the individual over time, each woman does tend to have a "central tendency in menstrual interval" (p.99, Treloar et al., 1967).

2.2.1.3 The parameters of menstrual bleeds: Volume, duration, and "shape"

Duration and amount of menstrual bleeding also vary, within accepted normal ranges. Both factors are difficult to measure as they rely on self-report, and therefore depend on shared understanding of experiences which are elementally individual. Volume is particularly vulnerable to the problem of making hypothesized comparisons with others. Because reactions to bleeding experience are very important to the acceptability of contraception, the World Health Organization (WHO) commissioned a multi-centred, multi-ethnic survey of the patterns and perceptions of vaginal bleeding (Snowden & Christian, 1983; WHO, 1981). A general survey was carried out on 5,322 women in 14 settings in ten different countries (Egypt, India [2], Indonesia [2], Jamaica, Korea, Mexico, Pakistan [2], the Philipines, the United Kingdom, Yugoslavia [2]). Approximately 500 parous, non-pregnant, non-lactating, non-menopausal women were interviewed in each setting, and a sub-sample of 10% were required to keep a daily diary of menstrual bleeding.

The incidence of bleeding, volume, duration, and "shape" were all determined from the general survey, and related to age, urban/rural residence, social status, literacy, contraceptive use, and breast-feeding activity. The world-wide modal duration of bleeding was 4 to 5 days. More Egyptian, Indian, and Mexican women reported 1to 3 day bleeds, while British, Indonesian, and Pakistani women reported 6 days or more. There was a tendency for urban women to report longer bleeds, and illiterate women short bleeds, however there was a lack of cross-cultural consistency. The majority of women reporting 1-2 day bleeds were over 30 years old, and also tended to have high parity. Oral contraceptors were much more likely than non-contraceptors or intrauterine device (IUCD) and injectable users to have 3 to 4 day bleeds, and less likely to have longer bleeds (Snowden & Christian, 1983; WHO, 1981).

The concept of volume of blood loss is tied to duration of bleeding. Throughout the world women reported their bleeding to be "moderate". Urban women were more likely to report heavier bleeds, but low status women were more likely to report extremes of blood loss. Contraceptive use was the only other factor which influenced

volume reporting. Pill users tended to have lighter bleeds than other contraceptors. The dynamics of bleeding over time, or the "shape", also related to method of contraception. Forty-five per cent of women reported bleeding heavily at the beginning of an episode, and more lightly towards the end. Thirty per cent start lightly, become heavy, and finish the episode with light bleeding. IUD users were more likely to have the later bleed shape, and OC users to have constant blood volume over the whole episode (Snowden & Christian, 1983; WHO, 1981). Studies involving the collection menstrual blood reveal that 78% of bleeding takes place on the first two days of menstruation, further it is estimated that 95% of women produce less than 60ml of blood during each period (Shaw & Roche, 1980). Women who bleed more than this are considered menorrhagic, or to bleed excessively (Abel, 1985; Smith, 1986).

In another large pooled multi-centred data set gathered in Europe, South East Asia, India, Pakistan, Latin America, Africa, the Caribbean, and China, WHO sought to relate bleeding patterns to regional, individual, and contraceptive factors (Belsey, 1988a, 1988b; Belsey, d'Arcangues & Carlson, 1988; Belsey, Peregoudon & Task Force on Long Acting Systemic Agents for Fertility Regulation, 1988). Overall they found that within a given method of contraception, bleeding patterns were more closely linked to geographical region than any other demographic or situational factor. The implication is that distinct cultural styles of reporting experience may account for some of the observed differences, even with the most carefully and uniformly collected data. There is evidence that the duration of menstrual bleeding changes over the seasons, with short bleeds in the summer and longer ones in the winter and spring, which might also contribute to differences across disparate geographical regions (Datta, 1960).

In summary, there is great variability in the length of the menstrual cycle and the duration and volume of bleeding episodes across women, and within women over reproductive life. The 28 day cycle is a myth. However, there are "normal ranges" for each of these parameters which are dictated by neuroendocrine functioning and by a variety of situational and constitutionals factors.

2.2.2 Bleeding During the Combined OC Cycle

> "Today there are millions of women on steroid contraceptives, programmed for artificial bleedings at approximately 28-day intervals. Thus from mythological ages, the cabala of numbers has joined, in modern times, with engineered manipulations of human reproductive physiology. In science, as in all human behaviour, fossils survive development." (p.5, Vollman, 1977)

The endocrinology, pill taking regime, and state of the endometrium during the OC cycle were all described above. This section concerns the effects of OCs on vaginal bleeding experience.

2.2.2.1 The physiology of withdrawal bleeding and pill cycle length

Given the evidence just presented, it is clear that the 28 day pill taking regime is a highly artificial imitation of the menstrual cycle. It does not seem that any survey was made during pill development of the bleeding pattern which women would prefer to experience while using the new steroidal contraceptives (Pincus, 1965). It has been argued that "incessant" ovarian cycling is a modern anomaly which runs contrary to the vast majority of human history in which several pregnancies, interspersed with long periods of lactational amenorrhoea ensured that menstruation was an infrequent event (Short, 1976). Nevertheless, rather than attempt to emulate pregnancy, for example, the pill cycle creates an idealized "menstrual cycle".

Instead of menstruation, pill takers experience withdrawal bleeding as a result of the abrupt removal of pill steroids. Because the endometrium has not been prepared in the usual way, and in the absence of a CL, bleeding begins as soon as the pill agents are cleared from the system. The delay to bleeding thus depends on the potency and clearance rate of, in particular, the gestagen. Generally, combined OCs produce a highly constrained cycle length with approximately four day withdrawal bleeds during the pill free interval, separated by 23 to 25 day intervals, thus generating 27 to 29 day cycles (Belsey, 1988a; Fraser, 1986). Bleed volume and duration are also very often reduced by the pill (Fraser, 1986; Snowden & Christian, 1983). Because the progestagen inhibits the proliferative effect of the oestrogen component there is simply not as much endometrium to be shed. In addition pill steroids may also desensitize the uterus to prostaglandins which are implicated in heavy bleeding and pain (Schering, 1989; Abel, 1985; Woods, Most & Dery, 1982). Oral contraceptives also reduce uterine tone, or pressure, and reduce the frequency and severity of contractions during withdrawal bleeding, all of which leads to a reduction of local ischaemia and therefore pain with bleeding (Ekström, Juchnincka, Laudanski & Åkerland, 1989; Schering, 1989).

2.2.2.2 Breakthrough bleeding on OCs

One important difference between bleeding in the pill cycle and bleeding in the menstrual cycle is that inter-cycle bleeding is far more common on the pill. A

proportion of women experience slight bleeding at mid-cycle in association with ovulation, however, in the absence of any uterine pathology it is rare at other times of the cycle (Vollman, 1977). Bleeding during active pill taking, on the other hand is relatively common and a small, but notable, percentage of women on the pill develop amenorrhoea, or "miss" some bleeds. It has already been pointed out that defining and collecting reliable information about bleeding experience is problematic. This may be why, although it is often cited as an important reason for pill discontinuation (eg- Bancroft & Sartorius, 1990; Belsey & Farley, 1988), there is relatively little information on the control of bleeding (Weijers, 1984). Incidence rates for so-called breakthrough bleeding (BTB) vary widely. Some factors responsible may be distinguishing between "spotting"[5] and BTB, variable reporting due to differences in menstrual equipment use, and correcting incidence rates for missed pills or past history of irregular bleeding (Weijers, 1984).

Most BTB seems to occur in early pill cycles, especially the first three months, whereas amenorrhoea increases with duration of pill use (Edgren, Nelson, Robert & Keifer, 1989; Fraser, 1986; Weijers, 1984). Increased progestagen dose reduces BTB, while EE dose seems to determine spotting. In a survey of 16 different trials, Microgynon generated a BTB rate of 2 to 18% of cycles, while Trinordiol had 24% in the first cycle and 12% in the 12th (Weijers, 1984). Fraser (1986) quotes a rate of 7.5% overall, but up to 25% if pills are missed. In a study in which 157 women were randomly allocated to one of three triphasic pills, the BTB rates were very high: 33% for Trinordiol, 44% for Tri-Norilyn, and 63% for Ortho-Novum 7/7/7 (Droegemueller, Katta, Bright & Boes, 1989). The authors suggest that the mid-cycle rise in oestrogen, and or the greater bioavailability of LNG may account for the lower incidence on Trinordiol. BTB has been found to vary over the cycle, being lowest on days 5 to 7 and 15 to 18, and highest on days 10 to 13, and 19 to 21 (Edgren et al., 1989).

The mechanism behind BTB is not clear. One possibility is that there is insufficient unopposed oestrogen present during the pill cycle to generate progesterone receptors uniformly throughout the endometrium. Therefore, some areas of tissue are not

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Spotting refers to very light bleeding, generally defined as requiring the use of one, or no, tampons or pads per day. The concept is unhelpful in settings like the Indian subcontinent, however, as women do not tend to use any menstrual equipment, no matter how heavy the bleeding (Snowden & Christian, 1983). Therefore, it is probably best to distinguish spotting from BTB only in industrialized settings where equipment use is common.

supported adequately by the gestagen in the pill, resulting in bleeding (Baird & Glasier, 1991). Alternatively, individuals may have different sensitivity to the pill steroids. There is evidence that "psychogenic" BTB can be induced if women are given a placebo and told it is an OC, and that they may expect to have BTB (Aznar-Ramos et al., 1969; Pincus, 1965). Thus while bleeding experience over the pill cycle is more highly constrained than during the menstrual cycle due to the rigidity of the steroidal inputs, individual and situational factors may still play a role.

2.3 Cyclical Changes in Emotional and Physical Well Being over the Menstrual Cycle

For centuries a variety of aspects of well being have been observed to alter alongside the more or less regular cycle of physiological changes and vaginal bleeding (eg- Rubinow, Roy-Byrne, Hoban, Grover & Post, 1985). This section is concerned with *what* features of well being fluctuate over the cycle, *when* these changes occur during the cycle, *who* experiences them and to what degree, and *why* women may have such, cycle-related experience.

The hallmark of the literature on cycle-related phenomena is that there are more uncertainties than certainties. The first difficulty is to define what is meant by cyclical change. The main reason for the difficulty is the vast heterogeneity of women's experience (Gise, 1988) which arises from the fact that every dimension that needs to be included in a definition varies across individuals and within them over time. These dimensions include the timing of changes, the degree or severity of change, the aspects of well being which change, and the level of consistency in timing, severity, and factors which are required to constitute "cyclical change". It is also important to distinguish between the different contexts in which variable well being is being considered, notably, in clinical practice, in research, or in the daily lives of women. In each of these settings the salience of the various aspects of cyclical change will differ.

While this thesis concerns changes in well being during the pill cycle, it is essential first to consider those changes which accompany the menstrual cycle, as background, and because of the potential aetiological significance of similarities and difference in well being patterns in these two endocrinologically distinct states.

2.3.1 The Problems of Defining Cyclical Change: The concept of the premenstrual syndrome

A multitude of factors have been observed to vary regularly in time with the menstrual cycle. Moos (1969) found that over 150 different symptoms and changes have been reported in the medical literature including such disparate phenomena as asthma, seizures, and vertigo (Rubinow & Roy-Byrne, 1984), along with more frequently cited changes in emotional and physical well being such as tension, irritability, depression, bloating, breast tenderness, and period-type pain. The concept of "premenstrual tension" or latterly, the "premenstrual syndrome" (PMS) was introduced in 1931 by a gynaecologist called Robert Frank (Moos, 1968) who attributed a clustering of negative moods and physical symptoms in the 7 to 10 days before menstruation to some dysfunction of the ovarian cycle, which he treated with ovarian irradiation. In the same year, Karen Horney described the same phenomenon which she attributed to repressed sexuality and difficulty in accepting the female rôle, and suggested that it could be dealt with through psychotherapy (Clare, 1989). The two important features of their concept of PMT or PMS is that 1) it is characterised by largely negative changes, and 2) these changes occur in the later half of the cycle, before menstruation.

The most rigid definitions of cycle-related change come from consensus attempts to create operational definitions which can be used to diagnose women who suffer from a clinically significant syndrome. For example, PMS has been defined as "the cyclic occurrence of symptoms that are of sufficient severity to interfere with some aspects of life and which appear with consistent and predictable relationship to menses" (Gise, 1988). In April, 1983 the National Institute of Mental Health (NIMH) in the U.S.A. recommended that for research purposes PMS be defined as occurring if a woman shows an approximately 30% change in one or more mood symptoms from the pre- to the postmenstruum, and if this is prospectively documented in at least two consecutive cycles. The premenstrual phase was defined as the 6 day interval before menses, and the postmenstruum as cycle days 5 to 10 (Hamilton, Parry, Alagna, Blumenthal & Herz, 1984).

Most recently the American Psychiatric Association (1987) has created the term "late luteal phase dysphoric disorder" (LLPD) in an effort to standardize the definition and classification of premenstrual syndrome (Warner, 1992a; Schnurr, 1989; Gise, 1988). LLPD has been entered in Appendix A of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R). The idea of LLPD has been

widely criticised both for the implications of associating a specifically female experience with psychiatric illness, and as a usable and valid research and clinical tool. For example, the criteria for LLPD require one to distinguish between women with predominantly mood versus physical symptoms, to exclude women who are experiencing another disorder which is exacerbated in the luteal phase, and to confirm symptoms prospectively over at least two cycles. There is no clear justification for dividing physical and mood symptoms, nor is the degree of change necessary for clinical diagnosis specified, nor the means of distinguishing "true" PMS from another disorder. On the other hand, it is stated that symptoms should remit within a few days of the onset of bleeding, which ignores a variety of other potential patterns of cyclical change (Warner, 1992a; Gise, 1988).

2.3.2 The Temporal Organization of Cyclical Phenomena

It is important to strive to standardize diagnostic criteria. Equally to develop a meaningful and comparable body of research, it is desirable to use similar and rigourous methodologies across studies. Much research in this area is methodologically flawed and these problems will be discussed further below. It has been proposed that PMS is less the presence of specific symptoms, than the temporal relationship of these variables to menstruation, notably "the premenstrual onset and postmenstrual offset" of which ever symptoms are troubling (Schnurr, 1989). While this idea may be helpful as a rough guideline it ignores the temporal complexity of symptoms across women.

In particular, authors like Katriona Dalton (eg-1983), who played a large role in popularizing the notion of PMS, emphasize that PMS symptoms must remit with the onset of menstrual bleeding. However, Dalton later revised her definition, introducing the concept of the "paramenstruum" which includes the four days before menstruation and first four days of bleeding (Rubinow & Roy-Byrne, 1984), and has generally used her own definition inconsistently in different writings (see Bancroft & Backstrom, 1985). And early research (eg- Moos, 1969) illustrated that so-called premenstrual symptoms could actually persist, or appear during bleeding itself. Asso (1983) rightly argues that the whole cycle should be studied and not just selected, and pre-defined phases around menses.

2.3.3 The Prevalence of Cyclical Changes or Premenstrual Syndrome

Walker (1987) discusses of the nature of "definition" further with respect to PMS, and proposes that rather than possessing narrowly definable features PMS is one extreme of the continuum of women's cycle-related experience. Although it is of theoretical importance to try and establish the boundaries of what is meant by PMS, this thesis is not strictly concerned with PMS, but with cyclical change in the broad sense. For example there may be regular oscillations in well being over the cycle which are not severe and which may not occur in the premenstrual or menstrual phase in particular, that may still form a relevant part of the individual woman's experience. The aetiology of cyclical change in well being, in whatever form, is not yet clear. It is therefore premature to impose rigid definitions and indeed limits the power of exploratory research in the area (Warner, 1992a). However, it is possible to gain an impression of the prevalence and the nature of cycle-related change in women. Almost all symptoms which have been linked to the menstrual cycle, and are included in the constellation of factors making up PMS, (with the possible exception of period pain) are common, non-pathological, subjective states which may be experienced from time to time by any healthy woman or man.

The prevalence rates for PMS or cycle-related change vary anywhere from 5% to almost 100% depending on the population studied and the way information about cyclicity is obtained and cyclicity defined (Metcalf, Livesey, Wells & Braiden 1990; Yuk, Juddutt, Cumming, Fox & Cumming, 1990; Stewart, 1989; Logue & Moos, 1988; Bancroft & Backstrom, 1985; van den Akker & Steptoe, 1985; Clare, 1983; Snowden & Christian, 1983; Woods, Most & Dery, 1982; Reid & Yen, 1981; Janiger, Rifferburgh & Kersh, 1972). However, it is widely agreed that only about 2 to 10% of women are severely affected by changes that may interfere with their functioning (for reviews see- Graham, 1989; Walker, 1987, 1992; Bancroft & Backstrom, 1985; Asso, 1983). The sorts of phenomena observed to fluctuate in a regular way over the cycle have been variously categorized as: psychological, somatic, and behavioural (Hamilton, Parry, Alagna, Blumenthal & Herz, 1984); pain, concentration, behaviour change, autonomic reactions, water retention, negative affect, arousal, and control (Moos, 1968, 1969); affect, cognitive, pain, neurovegetative, autonomic, central nervous system (CNS), fluid/electrolyte, dermatological, and behavioural (Rubinow & Roy-Byrne, 1984); and systemic changes, bodily changes, nervous system changes, and

psychological and behavioural changes (Asso, 1983). All of these typologies cover essentially the same aspects of well being.

The number of specific, "common" cycle-related symptoms indicated ranges from about 20 to about 50 (Rubinow & Roy-Byrne, 1984: 42 symptoms; Hamilton et al., 1984: 22 symptoms; Moos, 1969: 46 symptoms). Clearly some of the distinctions drawn between different symptoms are semantic, and may not actually reflect meaningful differences in experience. For example, such negative affect symptoms as tension, anxiety, irritability, anger, restlessness, dysphoria, depression, sadness, etc. may not describe anything more than negative mood with probable outwardly directed, and inwardly directed components. Nevertheless, efforts have been made to separately quantify many of these symptoms.

Walker (1987) has tabulated symptom prevalences across ten different investigations which used the same terms to describe particular states, including: irritability, depression, breast changes, abdominal bloating, and period type pain. All symptoms but period pain had the greatest mean prevalence in the premenstrual phase of about 50 to 60%, followed by the menstrual, about 20 to 30%, and postmenstrual phases, about 0 to 20%. Period pain was most frequent in the menstrual, and then premenstrual phase. Fifty per cent of women studied reported menstrual, and almost 40% premenstrual, period pain. With relatively few studies distinguishing severity, and possible overestimation due to retrospective report (see below), it is clear that these changes are very common.

Woods, et al. (1982) conducted a general population survey of 179 U.S. women of different races, ages and socioeconomic status (SES) using the Moos menstrual distress questionnaire (MDQ- 8 symptom factors described above). More than 30% of the sample reported weight gain, acne, breast tenderness, irritability, mood swings, depression, and tension mainly premenstrually, and tension, backache, fatigue, and period pain mainly menstrually. Headaches and anxiety occurred frequently, but were not associated with a particular cycle phase. Only 2 to 8% of symptoms were reported as severe or disabling, except menstrual period pain (17%), and premenstrual and menstrual irritability (12%). Other retrospective surveys and reviews have reported similar patterns (Stewart, 1989; Logue & Moos, 1988; van den Akker & Steptoe, 1985; Asso, 1983; Clare, 1983; Sheldrake & Cormack, 1976; Janiger, Rifferburgh & Kersh, 1972) with mood changes clustering premenstrually, and physical changes menstrually.

While some authors report, as do a proportion of women themselves, that there are changes in cognitive ability and performance associated with the menstrual cycle the preponderance of findings fail to support this belief. This relationship has been well reviewed by Sommer (1973, 1992). Nevertheless there is some evidence that central and autonomic nervous system function do alter over the cycle, which may potentially mediate changes in well being. The two systems seem to vary independently over the cycle, with CNS activity higher at mid cycle, and autonomic activity highest premenstrually (Asso & Braier, 1982; Asso, 1983). Some consequences of these variations are increased premenstrual susceptibility to adverse conditioning, and differences in the distribution of REM sleep and possibly in the content of dreams (Asso, 1983).

2.3.4 Positive Perimenstrual Changes

At least since the introduction of the concept of PMS, there has been a profound emphasis on the negative aspects of cyclical change. Several authors have challenged the idea that the perimenstruum is characterized by entirely negative experience. Logue & Moos (1988) reviewed the literature on the prevalence of positive changes premenstrually, and found that between 5 and 15 % of women experience increased excitement, energy, and well being, and there are also reports of increased activity, heightened sexuality, and improved performance on certain tasks. The arousal scale on the MDQ (Moos 1968, 1969) includes the positive scales: affectionate, orderly, excited, well being, and bursts of energy. About 20% of women have mild to moderate arousal premenstrually, 5% have high arousal, which is linked to low scores on the other symptom factors (Logue & Moos, 1988).

Parlee (1980, 1982) has proposed that some women may experience a "premenstrual elation syndrome" in which a premenstrual increase in general neuro-psychological activation is translated into positive sensations and feelings. Schachter & Singer (1962) have demonstrated that moods are expressed differently depending on the individual's background emotional or environmental state. The expression of negativism may also be somewhat culturally dependent; for example, food craving is considered a positive, not a negative, symptom by Indian women (Chaturvedi & Chandra, 1989). If women have higher activation premenstrually they may attend to stimuli less selectively and may recognize emotional information better (Logue & Moos, 1988). Stewart (1989) gave 100 consecutive Well Woman clinic attenders a retrospective questionnaire to complete which contained a list of 25 negative and 14 positive cyclical changes. Sixty-

six per cent of women reported at least one positive change, including increased sexual interest and enjoyment, greater tidiness, more efficiency, more attractive breasts, and increased energy and creativity. It seems likely that failure to observe positive perimenstrual changes in many studies stems from the failure to ask women the right questions and the traditional emphasis on negative experience which may limit the nature of reporting.

2.3.5 Symptom Severity as a Predictor of Prospective Confirmation: Physical versus Mood Changes

It is now well established in menstrual cycle research that retrospective questionnaire surveys of the pattern and prevalence of perimenstrual symptoms may overestimate them to a large degree compared with prospective symptom records (eg- Halbreich & Endicott, 1985a, 1985b; Rubinow & Roy-Byrne, 1984; Rubinow, Roy-Byrne, Hoban, Gold & Post, 1984; Endicott & Halbreich, 1988, 1982). The number of women affected, the severity of symptoms, and the close temporal relationship of symptoms to menstruation all tend to be over-emphasized retrospectively. Parlee (1974) suggested that retrospective accounts, from both women and men, elicit stereotypic beliefs about how women feel over the menstrual cycle rather than producing an accurate description of experience. The likelihood of "confirmation" by prospective ratings seems to depend on a number of factors (Endicott & Halbreich, 1982), one of which is the severity of the perimenstrual change (Cumming, Cumming, Krausher & Fox, 1991; Coleman, Hart, & Russell, 1988).

Physical symptoms in particular are more likely to be confirmed prospectively, and seem to affect more women irrespective of whether or not they experience marked emotional changes (Metcalf, Livesey, Wells & Braiden, 1990; Coleman, et al., 1988; Slade, 1984; Asso, 1983; Snowden & Christian, 1983; Golub & Harrington, 1981; Janiger, et al., 1972). For example, Metcalf, et al. (1990) prospectively monitored 44 women who were self-selected for experiencing PMS (+), and 48 women who did not believe they had PMS (-) over two or three cycles. Using time series analysis on the data they found that 81% of PMS+ women had significant trends in physical symptoms over the cycle versus 33% of PMS- women. Further these swings were significantly more likely to be in the premenstrual phase in the PMS+ women, and to be more severe. While in a previous survey of these women (Metcalf, Livesey, Wells & Braiden, 1989) they found that cyclical moods were only evident in the PMS+ group. The most clearly cyclical changes in both groups were breast tenderness, bloating, and

food craving. The authors conclude that "premenstrual dysphoria [is] not an intrinsic part of the menstrual cycle, but [is] typical only of women with PMS" (p.203, Metcalf, et al., 1990). Physical symptoms are also more likely than moods to occur independently of one another (Warner & Bancroft, 1990).

Using the MDQ prospectively, and spectral analysis Coleman, et al. (1988) also found that for most women physical symptoms had a 28-day peak while only about one half of cycles showed 28 day peaks for depression, behavioural change, tension, and cognitive symptoms. The authors hypothesize that the reason for the difference in the incidence of various symptoms may be that as PMS becomes more severe more symptoms become manifest, thus physical and depressive changes are revealed at lower severities. Others attempting to factor analyse the experience of women who do and do not report cyclical change found that on the premenstrual assessment form (PAF; Halbreich, Endicott & Schacht, 1982) only 20% of non-PMS women did not meet the criteria for at least one negative syndrome (Yuk, et al., 1990). And that the factors found for a group of women (n=109) with prospectively confirmed PMS were similar in quality to non-PMS women (Cumming, et al., 1991). The two groups were distinguished by severity, and the authors conclude that PMS is simply part of the continuum of normal experience.

2.3.6 Individual Characteristics Predictive of Cyclical Change

A variety of investigations have focused on possible demographic or other determinants of cyclical change. These include age (older women- more PMS: Golub, 1988; Snowden & Christian, 1983; Asso, 1983), parity (higher parity- more PMS: Warner & Bancroft, 1990; Asso, 1983), cycle length (irregular cycles- more PMS: Rubinow & Roy-Byrne, 1984; Woods, et al., 1982; Sheldrake & Cormack, 1976; Coppen & Kessel, 1963), work (women who work outside home- less PMS: Bancroft & Backstrom, 1985; Asso, 1983; Woods, et al., 1982), marital (married women- more PMS: Bancroft & Backstrom, 1985; Paige, 1973), or socioeconomic status (negative relationship of PMS to education and income: Woods, et al., 1982), culture (different symptoms in different racial groups: Janiger, et al., 1972), religion (orthodoxy in Judaism and Catholicism- more PMS: Paige, 1973), history of sexual abuse (severe sexual abuse- more common in PMS patients than controls: Jensvold, Muller, Putnam & Rubinow, 1989), and personality or psychiatric health (neuroticism, psychosis, and past history of depression- increased propensity for, or exacerbation of PMS: Warner,

Bancroft, Dixson & Hampson, 1991; Morse & Dennerstein, 1988; Mira, Vizzard & Abraham, 1985; Bancroft & Backstrom, 1985; Clare, 1983; Coppen & Kessel, 1963).

The incidence of PMS is classically cited as being highest during the mid thirties, in women with children, and some authors suggest that there is a shift from the menstrual onset of symptoms in young women to more prolonged symptoms with a premenstrual onset (Golub, 1988; Snowden & Christian, 1983; Asso, 1983). However a number of studies have failed to show a positive relationship of symptoms to age, parity, cycle regularity, marital status, or socioeconomic status (SES) (Simpson, Shand & Nyhof, 1988; Woods, et al., 1982; Coppen & Kessel, 1963). Warner & Bancroft (1990) have related cyclical change to the number of years of "natural cycles" a woman has undergone uninterrupted by pregnancy or oral contraceptive use, etc.. They have shown that women who have had between three and six years of natural cycles are more likely than women with fewer than 3 or more than 6 to report significant perimenstrual changes which are not attributable to stress, which may account for the equivocal findings of other studies. In particular, they indicate that parous women in their mid-thirties are most likely to seek help at a PMS clinic, suggesting that their life circumstances make coping with their cyclical change difficult. Overall, there is little consensus about which variables are predictive of cyclical change, which probably arises from the heterogeneity of women's experience, and the variety of different groups of women studied and methodologies used.

2.3.7 Cycle to Cycle Variability

Another important feature of cyclical change with methodological, diagnostic, and treatment implications is the variability of symptom patterns from one cycle to the next in the same woman. It has been suggested that inter-cycle inconsistency may be a defining characteristic of PMS (Warner, 1992a; Walker, 1991; Schnurr, 1989). The limited number of studies that have attempted to quantify the degree of inter-cycle variability have been reviewed by Walker (1991) who assessed the comparability of self-ratings over consecutive cycles in pill and non-pill takers and found that in a non-PMS Clinic sample most variables were consistent across cycles and cycle phases. Schnurr (1989) on the other hand who assessed women seeking treatment for self-reported PMS found very low consistency. And others (eg- Simpson, et al., 1988) have found symptom patterns to be very labile in both PMS, and non-PMS reporters, such that one third of a sample of 117 women showed different patterns in different cycles indicative of "chronic", "cyclic", or "acyclic" symptoms. This suggests that one

cycle of either retrospective or prospective data is not sufficient to establish the nature or severity of a woman's cyclical experience. Indeed, using only one cycle to establish 'cyclicity' is conceptually meaningless.

2.4 Aspects of Well Being which Change in Relation to the Pill Cycle

It is clear that certain aspects of well being vary in a regular fashion in relation to the menstrual cycle in a significant proportion of women. Yet an estimated 5% of women of reproductive age worldwide do not have a menstrual cycle because they use oral contraceptives (Kols, et al., 1982), and in Britain 23% of women aged 16 to 49 are using the pill for contraception (Guillebaud, 1991). If OCs have systematic positive or negative effects on cyclical symptom experience, they will influence a large number of women. Further, because the endocrine state which exists in pill taking is quite distinct from ovulatory menstrual cycles, the effects of the pill on subjective state may provide valuable information about the aetiology of cyclical change.

One difficulty with the study of OCs is that one must distinguish between pharmacologic 'side effects' of exogenous hormones, and persistent cyclicity in subjective state. In addition, different gestagens or dose regimens may produce different subjective responses. Factors such as duration of pill use, sense of contraceptive security, high discontinuation rates due to side effects or fear of side effects, and the personality characteristics of women who choose to take the pill, may influence experience, and ought to be considered in studies of well being and pill use. While the pill is one of the most researched drugs in history, there is still surprisingly little research on psychological associations (Pincus, 1965).

Early anecdotal reports and uncontrolled, retrospective, studies indicated that OCs largely improved, or eliminated cyclical change in well being (Richardson, 1992; Bancroft & Sartorius, 1990; Graham, 1989; Glick & Bennett, 1982; Reid & Yen, 1981). Many early studies were predominantly concerned with efficacy and the incidence of side effects, and the means of eliciting and reporting the prevalence of changes in well being were crude (Graham, 1989). Bancroft & Sartorius (1990) note that the method of eliciting OC 'side effects' influences rates observed and effects particular symptoms more than others, for example, depression. The incidence of side

effects can be up to four times higher when probing versus non-probing approaches are used.

Ideally, randomized, double-blind, placebo controlled prospective studies would reveal the incidences of both side effects and cyclical change. However, this methodology removes the important effects of personality, and expectations and attribution to the pill as a method of contraception (Bancroft & Sartorius, 1990). Reviews show that the discontinuation rate for OCs at 6 to 12 months varies from 25% to 75%. The contribution of side effects to discontinuation has important implications, not least for the prevalence of changes in well being in those women who persist with pill taking. The following discussion of the literature will be organized according to research methodology. The findings of recent retrospective studies of the incidence of cyclical symptoms in pill and non-pill taking women will be considered, followed by open prospective studies, and double-blind placebo controlled studies.

2.4.1 Retrospective Surveys of Symptom Prevalence on OCs

A number of studies which have simply compared women who take the pill with those who do not, regardless of pill type, have found little difference in women's self-reported cycle related experience. In a large survey of about 3300 university students, Sheldrake & Cormack (1976) found few differences between the 756 pill users and non-users. Pill takers reported less backache, period type pain, and irritability, but more depression and tension. In a recent, smaller survey of students, Richardson (1992) found a similar pattern with less breast tenderness and cognitive impairment, but more depression and crying reported by pill users. As women were only asked about symptoms during the premenstrual phase the results are not directly comparable with the previous study. Women taking the pill for more than two years had fewer symptoms especially during bleeding (Sheldrake & Cormack, 1976). This is consistent with the idea that women with a tendency to cyclical symptoms discontinue pill use, and relates to a finding that non-pill users over the age of 25 have more premenstrual mood symptoms, particularly sadness and anxiety, than women still using the pill at this age (Golub, 1988).

In a random sample survey with 24% pill takers, the only differences found were less premenstrual and menstrual acne and period type pain in pill users (Woods, et al., 1982). Women were questioned about any change from their pre-pill experience, and

34% reported a slight to large decline in physical symptoms on the pill, and 34% indicated no change, or a slight increase or decrease in psychological symptoms. Stewart (1989) found that pill taking Well Woman clinic attenders did not differ from non-users in the number of positive, negative, or total number of changes reported, but that there was a nonsignificant tendency for pill takers to have fewer positive changes. In another Well Woman clinic sample in which 101 pill takers were compared with 149 non-pill takers on the PAF, both groups had a similar number and severity of symptoms overall. Pill takers had somewhat less severe anxiety, fatigue, low mood, water retention, and impaired social function. Pill type and duration of use were not related to cyclicity, but past problems with the pill predicted more frequent and severe symptoms. Pill takers' symptoms were more likely to occur just before bleeding than non-pill takers' (Graham & Sherwin, 1987). In a further general practice survey no differences were found between pill and non-pill takers in Modified MDQ status, but pill takers did tend to have less severe symptoms. Concurrent psychiatric problems were related to more severe MMDQ scores, but duration of pill use did not influence scores (Clare, 1983).

A few large retrospective surveys have attempted to relate cyclicity in OC users to the type of formulation used, age and parity, and genetic factors. Warner & Bancroft (1988, 1990) surveyed over 5000 *Woman* magazine readers about their cycle related symptoms using a Menstrual health Questionnaire (MHQ) which asked respondents to assess their symptom experience over all phases of their most recent cycle. They compared the symptom report of a sample of 4112 women using either monophasic or triphasic pills, or not using the pill (Warner & Bancroft, 1988). Well being and sexuality covaried in the non-pill users, and was lowest premenstrually and highest postmenstrually. The OC users had a broadly similar pattern, but less marked peaks and troughs. Triphasic takers were more similar to non-pill users than monophasic takers, who tended to have more symptoms during bleeding, suggesting a more marked withdrawal effect.

There was a high rate of PMS self-report in this sample, 61%, probably because the questionnaire followed an article about PMS. They found that pill takers were less likely to report PMS than non-pill takers (Warner & Bancroft, 1990) especially if nulliparous. Amongst young nulliparous women the highest rate of PMS reporting was in ex-pill users, and young women were more likely than older women to have discontinued OCs due to side effects. Forty-one per cent of current pill users timed the

onset of their PMS to the present episode of pill use. These findings suggest two important points: 1) pill use and PMS are not mutually exclusive, and 2) PMS sufferers may be more likely to have an adverse reaction to OCs. Thus studies of women who are well established on the pill are likely to be composed of individuals with few cyclical changes, or for whom the pill improves moods and physical changes (Bancroft & Sartorius, 1990; Reid & Yen, 1981).

Another large survey assessed the genetic versus environmental component of psychiatric side effects to OCs using a large twin register in Australia (Kendler, Martin, Heath, Handelsman & Eaves, 1988). Seven hundred and fifteen monozygotic and 416 dizygotic twin pairs with similar OC histories were questioned about specific side effects experienced on the pill. Two-thirds of the sample were ever-users, and 80% of these had used the pill for at least one year. Thirty per cent were using the pill when surveyed. The following rates of side effects were seen in ever-users: 36% weight gain, 23% irritability, 18% depression, 16% bloating, 14% nausea, 13% bleeding disturbances, 3% acne. Based on their analyses the authors conclude that genetic factors play a clear role in pill induced weight gain, bloating, and depression, and possibly irritability, such that " 'suggestion', 'scapegoating', and confusion about the maternal role" (p.158, Kendler, et al., 1988) cannot be the sole factors responsible for OC related side effects. This study gives important information about the biological propensity to respond adversely to the pill, but unfortunately does not specify the severity, duration, or temporal pattern of symptoms, neither does it delineate pill types, though it is likely that it pre-dates the widespread use of low dose pills.

2.4.2 Prospective Studies of the Effects of OCs on Well Being

As with the menstrual cycle, the certainty of symptom report in retrospective accounts of pill takers is not always matched in prospective studies. Several recent studies have found no difference in the prospective negative symptoms of pill versus non-pill takers (Almagar & Ben-Porath, 1991; Alexander, Sherwin, Bancroft & Davidson, 1990; Slade, 1984). Yet pill takers reported more positive affect (Almagar & Ben-Porath, 1991), and more satisfying and active sexual relationships (Alexander, et al., 1990). Almagar & Ben-Porath (1991) conclude that these differences are due to the fact that pill takers have secure contraception, no fear of physical symptoms during bleeding, better relationships, and different personality traits. Two single case studies have shown that OCs can relieve psychiatric illness, psychotic episodes and clinical

depression respectively (Feltous, Rubinow & Conroy, 1980; Roy-Byrne, Rubinow, Gold & Post, 1984). Roy-Byrne, et al. (1984) propose that the antidepressant effect could be mediated via steroid induced CNS receptor changes.

The variability of response to OCs is illustrated by a comparative study of women starting the pill (n=152) or a barrier method (n=40) (Herzberg & Coppen, 1970). Questionnaires about side effect experience were administered pre-pill, at 5 weeks, and 5 and 11 months. By 11 months 20% of women had stopped the pill due to headache, depression, irritability, weight gain, bloating, loss of libido, fatigue, nausea, or the wish to become pregnant. Of those continuing, pill takers showed a transient increase in bloating, headache, and nausea, but less depression, irritability, and period type pain at all time points. Clearly these findings cannot be taken as evidence that the pill resolves cyclical change since many women discontinued due to worsened symptoms. Of those women who became depressed on the pill, 47% had reported prior premenstrual depression, versus 27% of the whole group. The application of this study's findings may be limited since six different high dose pills were considered simultaneously, and assessment of well being was infrequent.

Other research has explored the effects of different gestagens, and more recently monophasic and triphasic pill regimes. Grant & Pryse-Davies (1968) assessed the monoamine oxidase (MAO) activity of endometrial biopsies in almost 800 women and related it and depression and loss of libido, to the oestrogen / progestagen ratio of high dose monophasic and sequential pills. They found the least breakthrough bleeding, but highest incidence of depression and loss of libido in high progestin / low EE pills. They found the lowest rate of mood side effects on the high EE sequentials. Overall, 16% of women experienced depression and / or loss of libido regardless of pill type. The authors proposed that progestin mediated rises in MAO in the endometrium might be mirrored by raised MAO in the CNS which has been implicated in the aetiology of depression. Although there is no objective evidence that MAO in the endometrium will parallel CNS levels this theory has been much repeated by subsequent authors (eg- Kane, 1976; Paige, 1971).

Progestagen dominated pills have been related to increased depression over the pill cycle (Forrest, 1979; Persky, O'Brien & Kahn, 1976). Forrest (1979) monitored 12 women established on a low dose pill for at least 3 months, over 30 days and found a steady increase in depression over the cycle, with a peak from pill days 11 to 19, or the

second half of the cycle. Bancroft, Sanders, Warner & Loudon (1987a) randomly allocated 114 women to begine taking either monophasic Microgynon, or triphasic Logynon and monitored well being daily over two or three cycles. A very large number of women dropped out due to study demands, which may compromise the generalizability of their findings. However, women on the triphasic (n=19) who had reported prior premenstrual mood change were more likely than monophasic takers (n=18) to experience lowered mood and loss of libido. Depression increased in the second and third weeks of pills, with relief in the pill free interval. While the timing is consistent with the previous two studies, the relationship to progestagen dose is not, since triphasics administer less gestagen than monophasics and are relatively EE dominated.

In a larger prospective comparison of various monophasic (n=35) and triphasic (n=30) takers versus controls (n=57), Walker and Bancroft (1990) showed that the symptom experience of pill and non-pill takers, and of pill takers who do and do not undergo an increase in gestagen dose over the cycle is very similar. The symptom profiles of triphasic takers were most like controls, yet all three groups were much the same except for breast tenderness. The monophasic takers had less premenstrual breast tenderness, and lower well being during bleeding. Bloating, period pain, and breast tenderness were all more clearly cyclical than moods. The authors conclude that ovulation is not necessary for cyclical changes in well being, but that a rise in progesterone at the end of the cycle is for breast tenderness. One difficulty with this study is that cycle phases were pooled and meaned across more than one cycle. This has the effect of emphasizing cyclical change around bleeding, while ignoring cycle to cycle variability in symptom scoring. These findings do not bear out the above conclusions that triphasic users are more likely to become depressed, or that a greater progestin / EE ratio generates more negative mood.

It seems that OCs may contribute to worsened mood or improved mood in a proportion of cases. Another possibility is that pill taking flattens out peaks and troughs in well being (Warner & Bancroft, 1988). Morris & Udry (1969) monitored the activity of 8 pill takers and 26 controls over one cycle using pedometers. While both groups had a mid-cycle peak in activity, pill users had a lower level overall. The pill group was small, and it is possible that the absence of oscillation is a result of taking the mean over the whole group. However, another study involving the content analysis of speech at four times over the cycle found that while non-pill takers had a U-shaped pattern of

negative speech content and ideation around bleeding, pill takers showed no cyclical mood fluctuation (Paige, 1971). Asso (1983) cites evidence that the pill takes "the competitive edge" off women's game playing, and that EE dominated pills make women more assertive and aggressive than progestagen dominated ones. She suggests that if the pill does cause a general flattening out of well being in women accustomed to marked fluctuation, this may be perceived as a loss of well being.

2.4.3 Double-Blind Placebo Controlled Studies of the Effect of OCs on Well Being

There have only been four double-blind, placebo-controlled studies of the pill and well being. The first involved only 8 women who were given either 2 cycles of Enovid plus 2 months placebo, or the reverse (Silbergeld, Brast & Noble, 1971). Volunteers were monitored using the mood adjective checklist, the MDQ, and interviews. All variables were maximal premenstrually or menstrually, but only physical symptoms were really cyclical, while moods showed a tendency to be worse premenstrually. During Enovid cycles women reported more nausea, breast tenderness, and bloating than on placebo, but less muscle stiffness, backache, and irritability. This study suffers from the small number of volunteers, and the large number of variables studied.

Another study (Morris & Udry, 1972) compared the day-to-day well being of 51 women randomly allocated to one of three high dose MES containing pills, or placebo. Volunteers were simply asked if they felt better, worse, or the same as usual. Placebo takers felt worst premenstrually, and on day 2 of bleeding (presumably due to period pain). Pill takers also felt worst premenstrually, but a proportion felt better or worse overall due to pill taking. The authors conclude that ovulation is not necessary for the occurrence of PMS, however, like the previous study, participants were not selected on the basis of PMS reporting. The study is weakened by the fact that there was no discrimination made between different symptoms, and all pills studied were high dose.

Cullberg (1972) recognized the difficulty of distinguishing pill side effects from the psychological effects of contraception, and cycle-related change in well being. He, therefore allocated approximately 300 women to one of three 50μg EE pills, or placebo for two months. Self-ratings and interviews were carried out before starting the tablets, and retrospectively after two months of pill use, and one month after stopping the pills. Volunteers were not told that they were taking an OC in order to control for the effects

of contraceptive expectations. Cullberg found that about twice as many pill takers had global adverse mental changes as placebo takers (approximately 34% vs. 18%). Premenstrual irritability and depression as assessed by the MDQ were not relieved by the pill more than placebo, but there was a trend towards less depression and irritability in gestagen dominated pills, and more in EE dominated ones. There was a higher frequency of adverse mood reactions in women reporting prior premenstrual irritability. This seems to support the idea that some women are inclined to adverse reactions. However, without prospective monitoring and baseline data, it is difficult to assess the degree of pill induced change in subjective state.

A fourth study has finally addressed some of the methodological problems inherent in the previous investigations. Graham & Sherwin (1992) selected women who were reporting PMS (n= 82 Clinic patients) and assessed them daily over one baseline month, before allocating them to placebo or the triphasic pill, Synphasic (7x 35μgEE+500μgNET, 9x 35μgEE+1000μgNET, 5x 35μgEE+500μgNET) for three months. The drop out rate was high, with 5 placebo takers stopping, and 18 OC users, 14 having had side effects. The most frequently reported side effects amongst drop outs were spotting, breast tenderness, and nausea, or other physical symptoms (Graham, 1989). Thirteen further women were excluded because they did not show prospectively confirmed PMS during the baseline month, and one who was anovular. Thus 20 pill takers and 25 placebo takers confirmed PMS and completed the study.

The authors found that both placebo and active medication reduced irritability and depression, while the pill was more effective in reducing breast tenderness, and bloating. Irrespective of mood, sexual interest was reduced in the pill group. There was no evidence that the timing of symptoms differed in the two groups, except for bloating which was shifted to the menstrual phase in the pill group. There was also no evidence that the placebo response diminished over the three months of treatment. The placebo effect on moods is to be expected as these women were told that they were being given "weak hormones" as a treatment for their PMS. The reduction in breast tenderness in the pill group may be exaggerated by the fact that many women with marked breast tenderness on the active treatment, dropped out. This study nevertheless shows that there is little significant difference in the cycle-related experience of women with known PMS when they take the pill (Graham & Sherwin, 1992).

2.4.4 Consensus on the Effect of OCs on Cyclical Change

It is not possible to make definitive statements about the way in which OCs influence subjective state. Differences in research methodology, many of which are also problematic in studies of the menstrual cycle, may account for some of the inconsistency. Variability in women's reactions to the pill are also responsible. Overall it would seem that a small proportion of women do have marked adverse reactions to the pill, reflected most often in depression and loss of libido (Bancroft & Sartorius, 1990), which may have a genetic basis. Women with a prior history of either PMS or psychiatric disorder may be amongst those most likely to have exacerbated symptoms on the pill. It is likely that these women discontinue pill use after a relatively short time. This fact is reflected in the higher rates of PMS reporting in past users of the pill. It also undoubtedly contributes to the apparently lower rates of severe cyclical change in current pill users, and may be in part responsible for the observation that pill use "flattens out" peaks and troughs in well being. Alternatively, flat affect may be pill induced mild chronic mood change which women do not attribute to the pill until they stop taking it (Bancroft & Sartorius, 1990). Equally, some women have elevated mood.

The importance of placebo-blind studies in the assessment of mood reactions is emphasized by the findings of both Cullberg (1972) and Graham & Sherwin (1992) who found equal changes in irritability and depression in pill and placebo takers. The question of how different pill formulations and dose regimens influence users remains unanswered. The relationship of progestagen dose, or ratio to EE, to subjective state is uncertain, with some studies suggesting that depression increases with increasing progestagen dose or a cyclical pattern of administration, i.e. triphasics (Forrest, 1979; Persky, et al., 1976; Grant & Pryse-Davies, 1968), some that depression decreases (Bancroft, et al., 1987a; Cullberg, 1972), and others finding no relationship (Walker & Bancroft, 1990). These studies may not be comparable because of differences in the actual gestagen studied, and high versus low dose oestrogen. While studies of high dose pills may be of aetiological interest, they are of questionable relevance to today's situation in which the vast majority use pills with low dose oestrogen.

In the pill cycle like the menstrual cycle, physical changes show more marked cyclicity in relation to withdrawal bleeding than do moods. A relatively large proportion of women seem to have improved physical symptoms, although certainly not everyone.

Some of the probably physiological mechanisms were discussed earlier in this chapter. To summarize, while pill use may filter out women with severe cyclical changes, there is no good evidence that cyclicity is abolished by pill use, or that the timing of specific symptoms is significantly altered. These facts make OCs a tractable model of the relationship of steroids to cycle-related change in subjective state.

2.5 Some Methodological Problems in Menstrual Cycle Research

It is only within the scope of this thesis to cover selected methodological questions. (See the following for methodological reviews- Warner, 1992a; Halbreich & Endicott, 1985b; Rubinow & Roy-Byrne, 1984). However, it will be clear from the above discussion that there are many uncertainties, inconsistencies, and sources of variance in cycle-related experience which present methodological problems for research. There are unresolved methodological issues about how cyclical change is defined, how data is gathered, which groups of women are appropriate for research, how data should be analysed, and how findings are ultimately interpreted. The question of defining cyclicity has already been considered, and relates directly to the inherent conflict in this field between the aims of research, and the desire to diagnose and treat women reporting severe and debilitating variations in subjective state. Attempts at clinical treatment have preceded real knowledge about the nature and the aetiology of cyclical change (eg- Warner, 1992a; Hamilton & Alagna, 1988) and have therefore largely failed. Further, they have led to the medicalization and pathologizing of the menstrual cycle such that a basic aspect of being female implies illness and has become susceptible to medical scrutiny and purported cure (Warner, 1992a; Clare, 1989; Laws, 1985).

2.5.1 Retrospective Versus Prospective Assessment

After the problem of definition, comes the question of the most valid way to gather information about cyclicity. The first problem of assessment is that by its nature it must be "subjective" and therefore may be confounded by such factors as context, emotional state, personality, attributions, expectations, study demands, beliefs, etc. (Warner, 1992a). When assessments are made retrospectively, as many as 50 to 80% of women who report "global PMS" fail to confirm this on prospective ratings (eg- Hamilton & Alagna, 1988). It is therefore argued that prospective, preferably daily, ratings of

symptoms over two or more cycles are required to establish the presence of PMS or other cycle-related cyclicity. However the validity of retrospection seems to depend on whether or not the information is gathered for the most recent cycle, or for the "average" cycle (Warner & Bancroft, 1990), and how the data are analysed[6] .

Some problems with prospective ratings are that they are demanding and therefore create selection bias through high attrition rates, there is no consensus about how to deal with inter-cycle variability, they are "noisy", and they may actually have a beneficial effect on the symptoms which they seek to measure (Warner, et al., 1991; Hamilton & Alagna, 1988). Retrospectives questionnaires have the primary advantage that they can be readily administered to a large number of women, yet they are clearly vulnerable to the effects of poor, selective, or biased recall in a way that prospective ratings are not. Prospective ratings do have the advantage that they can be related to concurrent measures like hormone levels, and cycle phases can be meaningfully, and consistently designated.

2.5.2 The Absence of Adequate Controls

Another basic problem is that there are no really adequate control groups for menstrual cycle studies. While captive catarrhine monkeys and apes, especially rhesus monkeys, chimpanzees, and gorillas, have been observed to undergo variations in behaviour over the menstrual cycle, such as restlessness and irritability (Janiger, et al., 1972), this information is not directly comparable to humans. Men are not adequate controls as they tend to live in close proximity to women and are therefore influenced by them. Non-menstruating women are poor controls as they will either be prepubertal, postmenopausal, pregnant, or possess some gynaecological pathology. Women who take the pill are likely to be highly selected, and may not in fact be a good control for the absence of a hormonal cycle (Asso, 1983). Thus this leaves women who do not report cyclical change, and women undergoing hormonal manipulations of some kind.

2.5.3 Sampling Bias and Experimental Demand

Because of the demands of prospective monitoring, samples are inevitably biased in favour of highly motivated women. Many studies also use captive groups like nursing and psychology students. The "college sophomore phenomenon" of conducting

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For example, Livesey, Wells, Metcalf, Hudson & Bates (1989) have found that in women reporting PMS the rate of confirmation is around 70% when time series analysis is used to detect cyclicity.

research on women aged 20 to 25 (Dan, Graham, Beecher, Bart, Komnenich, Krueger, Pital & Ruble, 1980) has the effect of biasing samples in favour of young, nulliparous women who are less likely to be experiencing notable variation in subjective state, particularly mood (Golub, 1988, Woods, et al., 1982). Knowing that a study concerns the menstrual cycle is also likely to affect the amount of cycle-related change observed. A number of studies concerning "experimental demand characteristics" have shown that attribution of negative mood and physical states to the premenstrual phase of the cycle is more frequent when women know the study concerns the cycle (Jarvis & McCabe, 1991; Englander-Golden, Sonleinter, Whitmore & Corbley, 1986; AuBuchon & Calhoun, 1985; Ruble & Brooks-Gunn, 1979; Ruble, 1977).

Parlee (1974) found that both men and women responded similarly to the Moos MDQ when men were asked to complete it describing the experience of women "in general", and women, their own experience. She concluded that both women and men respond in terms of stereotypic beliefs about menstruation and the cycle. Stereotypes are defined as:

> "[G]eneralizations about specific groups on which there is considerable social consensus and little or no supporting data....[B]eliefs seem to be more strongly held by those with little opportunity to acquire falsifying information (i.e. men[7], *my emphasis*) and to be formulated in such a way as to justify the social distance arrangements prevailing in the society." (p.240, Parlee, 1974)

In a now classic experiment, Ruble (1977) told women they were immediately premenstrual, or not to expect a period for 7-10 days using a sham EEG. Others were given no information about cycle phase. MDQ scores in the "premenstrual" group were significantly higher for water retention, pain, change in eating habit, and sexual arousal than the other two groups. Negative affect was not significantly different by group, which may reflect the fact that this was a University student sample. The author attributes the findings to stereotypic beliefs. Yet the "control" women were more similar to the "premenstrual" than the "intermenstrual" group. All women were actually within 6 or 7 days of a bleed, and it is possible that rather than reflecting false attributions amongst the "premenstrual" group, the findings show the tendency for the women who thought a period was over a week away to discount that their physical sensations were related to an impending bleed.

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7 Parlee (1974) found that men often reported 'symptoms' to be more severe than women did.

However, the notion of false attribution is supported by prospective studies in which the menstrual focus of the research was concealed (Aincough, 1990; Slade, 1988; Slade, 1984). In a study of 118 student nurses completing the MDQ daily for eight weeks as part of a "general health study", Slade (1984) found that only peaks of pain and water retention were located before or during bleeding, while emotional changes occurred randomly over the cycle. It was concluded that negative experiences were attributed to the biological influences of the perimenstrual phase, while positive experiences are more often attributed to other variables. Morse & Dennerstein (1988) conducted a prospective study of women seeking treatment for PMS, and also found that quite a lot of psychological symptoms occurred during the follicular phase. In contrast to Ruble (1977), they concluded that sensitivity to pre-existing symptoms changes during the luteal phase to generate PMS. The picture is further complicated by findings that women in another study who showed no prospective evidence of cyclical mood change, nevertheless reported PMS-type experience when asked retrospectively about the past two months during which they collected diaries (Aincough, 1990).

2.5.4 The Complexities of Analysis

In addition to the uncertainty of how best to gather valid data is the question of how to analyse it. Given a high degree of inter-individual variation it is of doubtful validity to summarize data using arithmetic means within women in arbitrarily defined cycle phases, and across women and cycles (Warner et al., 1991; Warner, 1992a). The uniqueness of women's experience may be of potential aetiological significance. Walker (1987) has summarized the purposes of analysis as follows: 1) to diagnose PMS, 2) to relate well being to change over time, 3) to relate well being to changing physiological state, eg- steroid hormones, and 4) to assess the efficacy of a particular treatment. The research reported in this thesis is primarily concerned with the second and third objectives.

Because of the implicit or explicit assumption that well being varies in relation to menstruation, analysis using conventional parametric statistics (eg- t-tests and Analysis of Variance, ANOVA) has tended to focus on establishing a statistically significant difference between the "premenstrual" and "postmenstrual" phases of the cycle (eg- 30% change described above) More recently analyses have centred on a variety of mathematically complex time series analyses (Livesey, Wells, Metcalf, Hudson & Bates, 1989; Schnurr, 1989; Magos & Studd, 1986) which take account of all data points over the whole cycle. A critique of these methods for use with daily self ratings

can be found in Walker (1987) or in section 6.4.6.1. It has been concluded that the method which one uses will continue to depend on the reason for which the data have been collected, eg.- for research or clinical use (Schnurr, 1989).

2.5.5 Symptom Subclasses

Yet another consideration is whether or not different women have different patterns of symptoms which suggest the existence of several menstrual cycle-related syndromes, and if there is a consistent factor structure of symptoms (Warner, et al., 1991; Cumming, et al., 1991; Yuk et al., 1990; Morse & Dennerstein, 1988; Halbreich & Endicott, 1985b). The PAF of Halbreich, et al. (1982) was developed specifically to sub-type perimenstrual change, but recent studies have found it ineffective at differentiating homogeneous research samples (Cumming, et al., 1991; Yuk et al., 1990). Further, factor analyses of different daily rating scales seem to produce different components in different samples, and to explain relatively little variance (Morse & Dennerstein, 1988; Sanders, 1981). Cyclical change characterized by depression may have a distinct aetiology (eg- Warner, et al., 1991; Halbreich & Endicott, 1985a; Rubinow, et al., 1985; Endicott & Halbreich, 1982). It has been emphasized because depression is a particularly troubling symptom which effects many women, and because relating cyclical change to affective disorder may shed some light on the aetiology of both conditions. However, efforts to separate different symptom experiences into sub-syndromes may be a spurious means of fitting data to unsubstantiated unitary, biological theories of aetiology (Walker, 1992).

2.6 Existing Theories of the Aetiology of Cyclical Change

A great many theories have been put forward to explain change in subjective state in relation to the menstrual cycle. In particular, much research has been directed at uncovering some physiological abnormality of the H-P-O axis or other concomitant biochemical change which would explain symptom experience. There is also a parallel, and often opposing, line of research which seeks social / psychological causes. Ultimately, it seems unlikely that either biology or psychology on its own is able fully to explain the variability of women's experience. There is a need for a genuinely integrated, and multifactorial approach to both the study and management of cycle-related change. Each of these positions will be considered in turn, before finally

discussing the possibility of a novel aetiological theory, which is the basis of the research undertaken in this thesis.

2.6.1 Biological Theories: "Raging Hormones"

Given the close temporal relationship of changes in well being to particular phases of the menstrual cycle it is not surprising that an aetiological link has been sought. Yet this area has been widely researched and repeatedly reviewed and the consensus is that no change or abnormality in any one hormone, electrolyte, neuropeptide, neurotransmitter, vitamin, etc. has been consistently associated with cyclical well being. Biological theories to explain mood and / or physical changes have included the following: oestrogen (excess), progesterone (excess, deficiency, or autoimmunity), altered timing of steroid dynamics, prolactin, aldosterone, renin / angiotensin, vasopressin, endogenous opioid peptides (endorphins and enkephalins), α-melanocyte stimulating hormone, glucocorticoids, androgen, insulin (hypoglycemia / increased glucose tolerance), melatonin, biogenic amines (serotonin, dopamine, norepinepherine), acetylcholine, vitamin B_6, magnesium, zinc, and prostaglandins (Walker, 1992; Graham, 1989; Walker, 1987; Bancroft & Backstrom, 1985; Hamilton, et al., 1984; Rubinow & Roy-Byrne, 1984; Backstrom, et al., 1983a; Clare, 1983; Reid & Yen, 1981).

The lack of substantiation for such theories is probably due to three causes: 1) methodological problems and inconsistencies, 2) basing theories on inferences about the potential actions or mediating power of substances in the menstrual cycle, and 3) failure to accomodate the complexity and variability of the phenomenon. In spite of equivocal evidence for all of these theories [or evidence that they only influence one particular symptom- eg. prolactin and breast tenderness (Andersen, Larsen, Steenstrup, Svendstrup & Nielsen, 1977)] many authors persistently argue that cyclical change must have a biological cause rooted in the menstrual cycle, and propose a variety of radical and potentially dangerous treatments which are probably no better than placebo, i.e. high does progesterone (eg- DeVane, 1991; Watson & Studd, 1990; Magos, 1989; Watson, Studd, Savvas, Garnett & Baber, 1989; Backstrom, et al., 1983a; Dalton, 1983; Osborn, 1981; Reid & Yen, 1981).

Bancroft & Backstrom (1985) describe a variety of ways of studying the biological basis of cyclical change. Three of these are of particular interest to the theoretical

consideration in this thesis; namely, looking at cyclicity in naturally anovular cycles, manipulating the hormonal cycle and looking for an effect on symptoms, and using hormones to produce symptoms. There is a good deal of evidence that cyclical symptoms can persist in anovular cycles, whether these are spontaneously anovular, or hormonally manipulated, like the pill cycle (eg- Walker & Bancroft, 1990; Walker, 1987; Bancroft, Boyle, Warner & Fraser, 1987b; Bancroft & Backstrom, 1985; Reid & Yen, 1981; Andersen, et al., 1977; Adamopoulos, Loraine, Lunn, Coppen & Daly, 1972).

However, as in pill taking, the nature of symptoms may be different in spontaneously anovular cycles. Backstrom, Sanders, Leask, Davidson, Warner & Bancroft (1983b) in a study relating steroids to well being, found that there were no mood changes in five anovular cycles, but there was cyclical breast tenderness and bloating. Since volunteers were not selected on the basis of severe mood change, it is not clear whether anovulation was responsible for the absence of mood changes, or whether this would have happened anyway. Walker (1987) has reviewed the evidence for cyclical change at the points of reproductive transition, around menarche, during and after pregnancy, and at the perimenopause, and concluded that too little information exists to assess whether cyclical changes occur at these times.

It has already been shown that cyclical symptoms can persist, and may even be worsened by the combined pill. Other information about the efficacy of induced anovulation comes from hormonal treatment studies, and from studies of women having hysterectomies with or without the ovaries conserved. Danazol is a synthetic steroid with anabolic properties that acts as a powerful anti-gonadotrophic agent and thus abolishes ovulation (Walker, 1992; Magos, 1989). In a double-blind cross-over trial of Danazol in 39 women with severe PMS, Danazol caused a significant improvement in depression, mood swings, irritability, tension, breast tenderness, pain, fluid retention, concentration, and behavioural change over placebo. However, 19 of the 39 participants dropped out of the trial. While only three are reported to have dropped out due to 'side effects', it is difficult to assess their findings with such high noncompliance (McKay-Hart, Hawthorn & Gilmore, 1985).

In a further double-blind study of 40 women with PMS, three different doses of Danazol or placebo were given daily for 3 months (Watts, Butt & Logan-Edwards, 1987). Only women who had prospectively confirmed PMS in 2 baseline cycles were

included. In the first treatment cycle most symptoms were improved by placebo, but by the third cycle 8 symptoms were improved on one dose of the active versus 3 on placebo. By the end of the trial more than 75% of women on Danazol were virtually free of breast tenderness, lethargy, anxiety, and increased appetite, but other, mainly mood and vasomotor symptoms were unchanged. Results were very variable for different women and different symptoms, and 13 women dropped out of the trial because they had experienced no improvement. It is possible that individual responses were due to variable degrees of gonadotrophin and steroid supression, but unfortunately endogenous hormones were not monitored in either this or the previous study.

Another synthetic agent able to generate "medical ovariectomy" is the GnRH (LHRH-a or GnRH-a) agonist. It is a new innovation introduced in the 1980's which works by desensitzing the pituitary to LHRH, and thus switching off the ovarian cycle. It has been shown to effectively abolish PMS symptoms when given by injection or subcutaneous implant. When given in nasal spray (Buserelin), there is a more variable respone (Walker, 1992; Magos, 1989). This may be due to poorer adsorption through this route, however most women have suppression of ovulation within the first one or two months of use (Bancroft, Boyle, Davidson, Gray & Fraser, 1985).

Bancroft, Boyle, Warner & Fraser (1987b) carried out an exploratory treatment trial of Buserelin with 20 PMS clinic patients and found that 10 women each had positive and negative reactions to it. Ovulation occurred in less than 10% of the 95 months monitored, and six out of eight of these were the first cycles of use. The drug tended to stimulate the H-P-O axis initially producing a worsening of PMS-type symptoms whether or not it was begun in the follicular or luteal phase. Four of the ten women with a positive reaction to Buserelin continued to bleed at regular intervals although they did not ovulate, while the other six were amenorrhoeic. These two groups did not differ on mood scores, yet those women who bled continued to have "premenstrual" physical symptoms, notably breast tenderness and bloating. The opposing reactions of different women who have confirmed cyclical changes is curious, and it is not clear whether the mechanism of action relates to steroid supression, gonadotrophin disruption, or some other drug mediated effect. GnRH analogues offer a valuable aetiological research model with which to abolish ovarian cycling without the re-introduction of steroids. Their usefulness for research however may not be matched by long term therapeutic use because they induce a state of hypo-oestrogenism and

therefore precipitate menopause type changes such as loss of bone density (Magos, 1989; Bancroft, et al., 1987b).

Another recent study has attempted to circumvent this problem by giving GnRH-agonist with replacement oestrogen and progestagen (Mortola, Girton & Fisher, 1991). Eight women with severe PMS were monitored over 9 months including 2 control months, 2 months with GnRH-agonist alone, four months of double-blind cross over with four different one month treatments, and one final control month. The steroid supplements included a month with GnRH-a and conjugated equine oestogen (CEE- as used in hormone replacement therapy) on days 1 to 25; a month with GnRH-agonist and medroxyprogesterone acetate (MPA) on days 16 to 25; a month with both of these; and a month with placebo alone.

The authors note a significant improvement in daily mood and physical scores in the luteal phase from the control months to the second half of the two unblinded months with GnRH-agonist. During the subsequent placebo month luteal phase physical symptoms remained significantly lower than control, but mood symptoms returned. And in the cycles where oestrogen and progestin were reintroduced alone both physical and mood symptoms returned to control levels. During the CEE+MPA cycle, moods were 60% better than control cycles, yet physical symptoms were not significantly improved. Nevertheless, the authors conclude that GnRH-agonist with or without replacement steroids is able to improve physical well being, yet only alone or with combined oestrogen-progestin does it improve moods.

The authors describe the reintroduction of "behavioural symptoms" in the placebo month as a "reverse placebo effect". What volunteers were told to expect during the steroid reintroduction phase is not stated, but the authors attribute the effect to "subjects' anticipation of worsening of symptoms during the estrogen and progestin administration" (p.252D, Martola, et al., 1991). The authors were also surprised to find that while placebo, CEE, or MPA alone reproduced symptoms to some degree but combined therapy did not. While the authors conclude that their findings are due to a lower dose of replacement hormone than a previous study which found PMS re-instated by hormone replacement therapy, the results are confusing and suggestive at best. The variety of difficulties with this study include the small number of women, the potential placebo effect of the unblind GnRH-agonist injections, the strong potential

carry over and order effects of the four steroid replacement months, and the potential confounding factor of different degrees of ovarian supression by the GnRH-agonist.

Other authors have claimed the success of oestradiol and progestin treatment for PMS without GnRH down regulation (Watson & Studd, 1990; Magos,1989; Watson, et al., 1989). Watson, et al. (1989) administered E_2 patches or placebo patches and norethisterone (days 19-26) in a double-blind cross-over fashion to 40 women with severe PMS. Both treated and placebo groups improved over the first three months of the trial, and women who started with placebo and changed to active treatment showed sustained improvement over three further months. However, women who started with active and changed to placebo treatment generally showed a decline in well being. Combined therapy of this kind abolishes ovulation, and the authors rather dogmatically insist that PMS can be completely eliminated by abolishing ovulation in this way. They attribute persistent symptomology to the high dose of cyclical progestin which is used to prevent endometrial hyperplasia. They note that "patients on active treatment had symptoms of premenstrual syndrome during the first few weeks of therapy, when normally they would be expected to be improving after menstruation" (p.731, Watson, et al., 1989). This appearance of follicular phase symptoms parallels the experience of women starting on GnRH analogues, and suggests an uncertain physiological effect of H-P-O suppression on symptom experience which may be of aetiological significance.

In spite of equivocal evidence, some authors believe so strongly in the role of ovulation in cyclical change that they espouse surgical castration if "medical ovariectomy" does not work (eg- DeVane, 1991; Watson & Studd, 1990; Magos, 1989). While such extreme interventionism is ethically and politically questionable, the effect of hysterectomy and ovariectomy on cyclical change do inform the aetiological discourse. There is now a good deal of evidence that cyclicity does persist after hysterectomy, although the timing and severity of symptoms seems to be changed by the absence of menstrual bleeding and the uterus itself (Walker, 1992; Metcalf, Livesey, Wells, Braiden, Hudson & Bauer, 1991; Walker, 1987; Osborn, 1981). This suggests the influence of some menstrual / uterine factor in cyclical change (Bancroft, Williamson, Warner, Rennie & Smith, 1992) and argues against the idea that cyclicity is entirely attributable to expectation and attribution to menstrual bleeding (eg-Osborn & Gath, 1990; Osborn, 1981).

While recent evidence suggests that bilateral ovariectomy does abolish symptoms, the results have been questionned due to the problems of phase definition without menstruation (Walker, 1992). Other problems for the design and interpretation of hysterectomy studies include timing in relation to surgery, dealing with individuals in possible ill health, controlling for operation-induced stress and disruption, and assessing placebo response. It is widely acknowledged that there is a substantial placebo response to treatments for cyclical change, but this does not seem to be considered in hysterectomy studies. The degree of placebo response is dependent on the perceived potency of the treatment, with 50% overall, 89% for tablets, and 94% for implants (Magos, 1989). Having allowed herself to be castrated to treat her PMS a woman has a tremendous incentive to be "cured". Further, since the placebo response tends to be more marked for mood than physical symptoms, and hysterectomy removes the major source of cyclical physical discomfort, the effect will appear that much more marked.

In summary, while there is evidence to suggest a biological component in cyclical change, no single biological cause has been identified. Certain consistent findings emerge from the variety of investigations in which the cycle is medically or surgically disrupted. They show that: 1) a proportion of women experience a significant improvement (eg- on OCs), 2) others find no change or show significant worsening, 3) PMS-type symptoms can occur in the absence of ovulation, and even in the hormonal conditions of the follicular phase, and 4) different symptom types, particularly moods and physical changes, respond differently to the ovarian cycle and its disruption.

2.6.2 Psychological and Social Theories for Cyclicity: "It's All in the Mind"

2.6.2.1 The female role, personality, and psychiatric illness

In parallel, and sometimes opposition to, biological theories are a number of theories for psychogenic causes of cyclical change. Historically, a psychoanalytic approach has been taken (Stout, 1989), and as the following quote shows this point of view is still active in some quarters:

> Blood and menstruation symbolize warmth, security, intercourse and satisfaction (Simpson, 1976) and have psychological links with childbirth, sexual relations and marriage. Frustrations or disappointments in these areas may be expressed through the menstrual cycle in the form of anxieties and morbid preoccupation, thus giving rise to symptoms. (p.107, Carney, 1980)

In this school of thought it is argued, for example, that women generate very irregular bleeding patterns in order "to communicate in a non-verbal pre-cognitive way" while women with slight "cycle disturbances" are using a "broader repertory of psychosomatic signals...to communicate their unhappiness" (Eder, Kemeter & Springer-Kremser, 1982). Early studies focused on relating PMS-type experience to neuroticism and to a failure to accept the traditional female social role. While psychoanalytic studies have found a relationship between role rejection and symptoms, studies using standard psychometric tests like gender inventories have tended to find the opposite, that symptoms are related to traditionalism, passivity, and inability to express emotions, particularly anger (Stout, 1989).

In a study which compared women seeking treatment for PMS, women with sexual dysfunction, and non-treatment seeking controls, women who scored highly for masculinity on the BEM gender inventory had high self esteem, internal locus of control, and more positive attitudes to menstruation, their bodies, genitals, and sex. While these women tended to be controls, there was no evidence that women reporting PMS differed from others in their attitude towards the traditional female role. Women with sexual dysfunction had the lowest self esteem, and the most negative attitudes, followed by PMS patients (Spencer-Gardner, Dennerstein & Burrows, 1983). In another, population based, survey of 179 women, sex role orientation and sex typing were not related to PMS reporting, while women engaged in more traditionally female occupations did report more severe perimenstrual negative affect (Brown & Woods, 1986). Slade & Jenner (1980) found in a group of young students that femininity was unrelated to symptoms but that women at the extremes of sex role attitudes, very traditional or egalitarian, were both more likely to report higher levels of symptoms during bleeding, but not premenstrually. They propose that both groups may dislike the reminder of their sex provided by bleeding.

Another theory is that negative attitudes towards menstruation may translate into negative labels for physical experiences and moods before and during bleeding, and/or emotions and behaviours which are considered out-of-role for women may be attributed to menstruation generating symptom experience in particular cycle phases (Jarvis & McCabe, 1991). The "cognitive labelling approach" to the study of emotions argues that the same bodily state can be described in different emotional terms depending on the external referents in the environment (Schachter & Singer, 1962). Parlee (1976)

argues that PMS may be conceived of as it is because hormone levels, rather than producing specific moods, alter "arousal levels" which are labelled negatively because of the social expectancies and negativism surrounding menstruation and femaleness. She notes that moods like irritability and depression have been culturally "highlighted...as the appropriate ones to feel in the premenstrual and menstrual phases".

Koeske & Koeske (1975) compared women's and men's negative attributions to the menstrual cycle using stories about a hypothetical fellow student in which her overall mood and the events in her day were construed as positive or negative. They found that female students were more likely to attribute emotionally expressive behaviour to the woman's personality and biology, than to extenuating circumstances in her environment. Inconsistencies between the tenor of mood and events produced more internal attributions, while if moods and events were consistent, moods were attributed to the events. Women are probably encouraged to make more negative self attributions than men because of different socialization (Asso, 1983; Dan, et al., 1980). In a study using the same sample as Brown & Woods (1986) above, the effects of menstrual socialization and stress on symptoms were examined (Woods, 1986). A stressful environment went part way to explaining cyclic symptoms, particularly negative affect. Socialization was related to attitudes towards the cycle, but not symptom experience. The degree of disability reported related directly to the severity of symptoms, again especially to negative affect.

It has been argued that awareness of cycle phase in relation to menstruation produces phase attributions (eg- Ruble, 1977). In a prospective study of cycle and non-cycle attributions, women taking the pill, who knew their cycle phase, made more cycle attributions during the premenstrual phase than non-pill takers. The non-pill takers made more attributions during bleeding, suggesting that fore-knowledge of cycle phase enables one to make premenstrual attributions of negative mood, etc. (Campos & Thurow, 1978). How such an attribution process works for individuals is not clear, for groups which might be expected to view menstruation more negatively, such as infertile women, show no evidence of worse cycle phase attributions (Slade, 1981). It is argued that attribution cannot be fully responsible for cyclical changes since women with PMS do not make more negative attributions to biological events than other women, and that PMS seems "to occur on a background free of psychiatric or physiologic illness" (p.1209, Reid, 1991).

The tendency to experience cyclic symptoms has been linked to certain personality traits and a history of psychiatric illness, namely neuroticism and affective disorders. Coppen & Kessell (1963) are often cited for making an early association between neuroticism and PMS. They found that even after controlling for the elements in the MMPI measure of neuroticism which might be confounded with PMS that a relationship persisted in women who reported irritability, depression, and tension. Neuroticism was not significantly correlated with irregular cycles or dysmenorrhea. The authors note that the relationship between neuroticism and PMS is not "simple" since not all neurotic women have PMS, nor do neurotic women whose neuroses improve with treatment necessarily loose their PMS.

Others have subsequently endorsed the relationship (eg- Bancroft, et al., 1992; Mira, Vizzard & Abraham, 1985; Slade & Jenner, 1980; Watts, Dennerstein & Horne, 1980), but have not addressed the important question of confounding. It seems that neuroticism is not just higher in the luteal phase in women with PMS, but over the whole cycle (Mira, et al., 1985), is related to prolonged perimenstrual depression (Bancroft, et al., 1992), and shows a stronger relationship with severe symptoms (Stout, 1989). State and trait anxiety have also been linked to cyclical change, and curiously "trait" anxiety which is held to be a constant personality factor was higher in the luteal than follicular phase in women with PMS (Mira, et al., 1985; Watts, et al., 1980). There is evidence that women with PMS are more likely to have type-A personalities, which make them more reactive and vulnerable to stressors involving a loss of control, eg. menstrual bleeding (Ussher, 1992).

There are three ways in which psychiatric illnes may relate to cyclical change. Existing illness may be exacerbated premenstrually or menstrually, PMS may mark a stage in the development of an illness such as depression, or cyclical mood change may be a distinct type of affective disorder which is entrained to the menstrual cycle (Stout, 1989). There are reports of menstrual exacerbation of psychosis, but PMS is not more common in psychotic women not having a current episode (Clare, 1983). Panic-anxiety syndrome, and bulemic episodes are observed to cluster at the paramenstruum (Rubinow, Roy-Byrne, Hoban, Grover & Post, 1984). In a general practice survey of about 450 women, Clare (1983) found that women with severe perimenstrual changes were more likely to have a current psychiatric problem, and that psychiatrically ill

women with PMS had more, and more severe mood changes, but not necessarily physical ones.

The depression seen with the menstrual cycle is most characteristic of "atypical" depression (Rubinow, et al., 1985), but has been described as quantitatively and qualitatively similar to major depressive disorder (Warner, et al., 1991). Warner, et al. (1991) have related the severity of premenstrual depression to a previous history of postnatal depression, and its duration (premenstrual and menstrual) to a history of treatment with antidepressants. The authors suggest two aetiological components of perimenstrual depression: 1) a menstrual cycle-related factor which precipitates severe premenstrual depression in "vulnerable" women, and 2) a general propensity to depressive illnes which generates prolonged cycle-related depressive changes.

2.6.2.2 Taboo, secrecy, and restriction: Attitude, belief, and behaviour

Menstruation and hormone withdrawal bleeding are not simply biological events; vaginal bleeding is political and polemical. Throughout written history the menstrual cycle and bleeding itself have been embued with social meanings, and have been the focus of many complex systems of belief and behavioural proscription. Its symbolism extends far beyond its physiological role. Menstruation has inspired a good deal of research based on the apperception that "[t]he belief system surrounding menstruation...is handed down from one generation to the next during the process of socialization" (p.53, Snowden & Christian, 1983), and the inherent knowledge that "[m]enstruation may not be important in itself, but it is highly symbolic of femaleness, and the ways in which people deal with it show us a lot about how women are viewed" (p.207, Laws, 1990). The idea that vaginal bleeding and its sequelae are culturally symbolic is fundamental to our understanding of the way in which women process and report their experience.

For the sake of argument, menstrual values can be viewed separately at the level of the individual and at the level of the society, although in practice they are elements of one another. Individuals are taught their menstrual values through gender socialization. This process has been described as "largely non-verbal, subtle, and indirect" (McKeever, 1984). For girls sexual socialization is difficult, contradictory, and largely negative emerging as it does from a social order in which female genitalia are either "eclipsed" or "exposed" (Ussher, 1989). Within this context communication between

mothers and daughters about sexual matters is generally "strained" and usually limited to a minimum of technical information about menstruation, and practical advice about hygiene (Matlin, 1987; McKeever, 1984). Martin (1989) notes that vaginal bleeding is portrayed in society, largely through the advertisement of menstrual equipment, as a "hygienic crisis". McKeever (1984) summarizes her assessment of the social position of menstruating women:

> "In conclusion, current social norms concerning menarche and menstruation emphasize cognitive understanding and proper use of sanitary devices to reduce fear of excretory soiling and successfully conceal all evidence from others. Thus the age old menstrual myths continue to influence attitudes and behaviours ensuring that a major characteristic of being a mature female remains a source of shame, embarrassment, and secrecy. (p.45)"

Individual families will approach the subject of menstruation differently, which is perhaps why simple sociological theories do not fully explain women's cycle-related experience. "Even within one society it is not possible to make simple statements about the meaning of menstruation. It is not a unitary phenomenon, not a single thing, socially; menstruation means all manner of things to all manner of people." (p.211, Laws, 1990) Information about the multifactorial nature of beliefs emerges from surveys of attitudes. For example, Brooks-Gunn & Ruble (1980) using the Menstrual Attitudes Questionnaire which included 33 statements with which women could agree or disagree, found five factors relating bleeding to: psychological and physical disability, a natural event, a bothersome event, a predictable event, and a non-event that does not or should not influence behaviour. They compared the beliefs of various groups including students, pre- and post-menarcheal girls, men, and older women. Overall, college women saw menstruation as natural, somewhat bothersome, but not very debilitating or predictable. Menarcheal girls and men perceived it as more debilitating than older women who were more likely to see it as a nuisance and a non-event.

The consensus of similar surveys and reviews is that bleeding is natural and womanly, and it is probably wrong or dangerous to interfere with it. On the other hand, it is embarrassing, a source of shame, should be concealed, is messy, and is troublesome when it causes symptoms (eg- Laws, 1990; Martin, 1989; Paige-Ericksen, 1987; Birke & Best, 1982; Brooks-Gunn, 1985; McKeever, 1984; Snowden & Christian, 1983; Brooks-Gunn & Ruble, 1980; Ruble & Brooks-Gunn, 1979; Paige, 1973; Berry & McGuire, 1972). Negative themes dominate. McKeever (1984) discusses a 1983

survey in which two-thirds of U.S. adults indicated that menstruation should not be discussed in the office or socially, and one quarter that it should not even be discussed in the home. She describes the system of restrictions surrounding menstruation active in Western cultures which includes restricted communication, altered activities, and concealment.

Paige-Eriksen (1987) describes the results of a survey of attitudes carried out for the Tampax Corporation in the United States in 1981, noting that men's and women's responses "appear to reflect an underlying belief about women's inferiority as persons" (p.176). For example, nearly all men and women replied that menstruation makes women more emotional, 89% of men and 66% of women that menstruating women do not function well at work, 66% of both sexes that women should conceal menstruation in social situations and 50% that women smell different while bleeding. And about a quarter to a third of people felt that menstruation affects women's ability to think, that physical activities should be restricted, that women look different, that period pain is psychological, and that women should not bathe or swim while bleeding. Twelve per cent of men and 5% of women even believe that menstruating women should stay away from other people.

2.6.2.3 The acceptability of induced changes in bleeding patterns

A small number of studies have explored women's willingness to eliminate bleeding for a time (Warner, 1992b; Jarvis & McCabe, 1991; Rutter, Knight, Vizzard, Mira & Abraham, 1988; Fraser, 1986; Snowden & Christian, 1983; Miller & Smith, 1975), and an equally small number have investigated the effects and acceptability of actually implementing such manipulations (Kornaat, Geerdink & Kiltsie, 1992; de Voogd, 1991; Hamerlynck, Vollebergt, Doornebos, & Muttendam, 1987; Loudon, Foxwell, Potts, Guild, & Short, 1977). The fears and support that women express for the prospect of induced amenorrhoea reveal a great deal about their fundamental beliefs about bleeding.

What all surveys of women's *willingness* to try eliminating bleeds have shown is that there is an inherent contradiction between their desire to eliminate the "hassle" and inconvenience of bleeding, balanced against a fear of the loss of an essentially female experience and a fear of health risks. Miller & Smith (1975) summarize that there is a "central conflict...between the potent loss of self image and the potential utilitarian gain", and go on to add that women possess a "prevalent normative structure" in

relation to bleeding experience. That is, women seem to have internalized boundaries for what they consider to be their normal experience which must function within the limits of what they imagine to be normal relative to other menstruating women. Experiences which deviate from these norms tend to cause alarm, and be unacceptable. This concept is consistent with the widely held view that one's menstrual experience is a barometer of reproductive and general health. A similar theme emerged from a comparative study of women seeking medical help for PMS, menorrhagia, or dysmenorrhoea. Rather than wishing to adopt a hypothetical treatment which eliminated their periods, these women wished for some treatment which would make their periods "normal" (Warner, 1992b).

In their early study, Miller & Smith (1975) found that 79% of women in their white, unmarried, nulliparous, lower to middle class sample would *very likely* or *possibly* eliminate bleeding if it could be done safely for a time. Jarvis & McCabe (1991) also found that 79% of their sample "would like to have their menstruation reduced". In an Australian study of women's attitudes and beliefs about withdrawal bleeding and their knowledge and beliefs about the pill, Rutter et. al (1988) found that about 45% of female doctors and patients had used the pill to alter the length of their cycle in the past. When women were asked how they would choose to take the pill if they could design their own pill regime about 50% said they would continue to bleed monthly, 24% 3-monthly, 4% 6- to 12-monthly, and 23% never. Yet apparently in direct contradiction, 83% of the same women said that it is necessary to bleed monthly while on the pill, and 69% that continuous pill use is undesirable.

In the WHO survey (Snowden & Christian, 1983) the fears that women expressed about induced amenorrhoea included fear of a loss of femininity, loss of fertility, loss of sexuality, loss of the reassurance of non-pregnancy, and loss of good health in that it would be unnatural, interfere with metabolism, and cause side-effects through the build up of "bad blood". Those women who would accept amenorrhoea tended to be young, educated, and urban, but would want to be certain that it would have no long term effect on health or fertility. The reasons that women in the Australian sample believed *withdrawal* bleeding to be important were similar: they allow the body to function normally, they copy what happens normally, they rid the body of waste, they prevent the womb lining building up, they let one's hormones settle down, they prove one's fertility, they prevent breakthrough bleeding, they allow one to avoid other symptoms, and they help to avoid cancer.

Thus a stated willingness to eliminate bleeding does not necessarily mean that a majority of women will actually do so, but equally a reluctance to try manipulating the cycle also does not mean that women will not tolerate such manipulations if they actually experience them. After all two of the most widely used methods of birth control world wide, hormonal contraception and interuterine devices, do alter women's actual bleeding experience. It would seem that within their personal "normative structure" women accommodate changes in their vaginal bleeding experience. The important implication of this process is that while novel contraceptive methods, or treatment strategies for cycle-related change, must take account of women's beliefs, with knowledge, support, and education novel approaches can be successfully introduced.

2.6.2.4 Silent bias in the social construction of the cycle and its research

Some authors have challenged the whole concept of PMS, and the illness model of the menstrual cycle as a misogynist product of the dominant, patriarchal ideology of Western society (eg- Ussher, 1992; Laws, 1990; Martin, 1989; Clare, 1989; Taylor, 1988, Rome, 1986: Sayers, 1986; Laws, Hey & Eagan, 1985; Koeske, 1983; Birke & Best, 1982). This, predominantly feminist, view does not seek to trivialize "biomedical fact", but seeks a more "complex, interactive" approach to menstrual cycle research and health care; it "challenges the view that science is disinterested and looks for linkages between beliefs about women and the social and political forces affecting women's lives" (p.2, Koeske, 1983). It is argued that "[s]cience...is used in our society to reduce discontent to biological malfunction." (p.125, Martin, 1989).

PMS is taken to be a social construction (Laws, 1985) which "...understood in the context of a patriarchal social order, ...is yet another ideological weapon used to define and control women" (p.15). Women are perceived as the "products and prisoners" of their menstrual cycle (Clare, 1989) such that their unhappiness can legitimately be viewed as consequence of their biology (Jarvis & McCabe, 1991; Laws, 1990, 1985; Koeske, 1983). A more practical argument for the modern emergence of the concept of PMS around the time of the World Wars, is that it provided a strategy for excluding women from the paid work force when the men returned:

> Women are perceived as malfunctioning and their hormones out of balance rather than the organization of society and work perceived as in need of a transformation to demand less constant discipline and productivity. (p.123, Martin, 1989)

> The symptoms of PMT which the doctors show most concern over- depression, anxiety and so on- are mental states which do not 'fit' with women's cultural created notions of ourselves as nice, kind, gentle, etc....[C]hange as such is not culturally acceptable. (p.35, Laws, 1985)

These concepts fit comfortably with the tabooed nature of the menstrual cycle in our society. As Douglas (1966) argues the degree of menstrual proscription in a society depends on the degree of men's security in their domination of women.

> ...[W]hen the principle of male dominance is applied to the ordering of social life, but is contradicted by other principles such as that of female independence, or the inherent right of women as the weaker sex to be more protected from violence than men, then sex pollution is likely to flourish. (p.142)

Douglas identifies that "[p]urity is the enemy of change, of ambiguity, and compromise" (p.162) which means theoretically that because women's bodies change, women cannot be pure. Indeed, historically women are an aberration of the real human model, the male (Jackson, 1985).

Most menstrual cycle research is carried out using a reductionist, ahistorical, and atomistic approach which claims to be value free using so-called "objective measures" which are "neutral" and relatively "error free". Thus biochemical variables are considered more "reliable and valid" and also causal than psychological and social variables (Walker, 1992). Yet an analysis of the language used in the medical and psychiatric literature reveals the "normative and correctional foundations of the scientific perspective" (p.3, Koeske, 1983). For example, the medical literature "...tends to underwrite the notion that women are less capable of meeting intellectual demands" with the use of terms like "confusion", "inability to concentrate", "lowered judgements", "forgetfulness" (pp.172-173, Birke & Best, 1982). [See Laws (1990) or Birke & Best (1982) for an analysis of the manner in which modern medical texts deal pejoratively with menstruation and women as menstruators.] Ussher (1992) lays the problem at the feet of researchers:

> [R]esearchers are rarely exposed; they remain shadowy figures identified only by name and institution, their assumptions and motivations clear only to themselves. This is an accepted part of the scientific discourse because researchers are conceptualized as objective, value-free rational observers. The very language that scientists adopt underlines their objective impersonal front, their presentaion of themselves as removed from any personal involvement in research activity. Their subjectivity, their own position within the scheme of things, is seen as irrelevant: Thus the researcher can remain on the outskirts, their pseudoanonimity protected by their very membership in the scientific elite. (p.144, Ussher, 1992)

Science is not above the stereotypic, and the means of extracting information as well as reporting it will reflect to a greater or lesser degree the stereotypic belief system (eg- Olesen & Woods, 1986; Laws, 1985).[8]

Biological explanations are not sufficient on their own to account for cycle-related experience, but current social and psychological theories also do not seem adequate to account for the irrefutable presence of some cyclical changes in some women. Can a negative societal view of women, bleeding, and the menstrual cycle really precipitate regular negative subjective states at a particular phase of the cycle? It seems likely that very severe symptoms or heavy bleeding may be associated with negative attitudes towards the cycle, and possibly more negative expectation and attribution to the perimenstrual phase. Perhaps some women do have a propensity to mental illness with facilitates negative cyclic changes. However, the evidence that cyclical change is linked to particular personality traits or social adjustment is suggestive but equivocal, and a causal relationship is not clear.

2.6.3 The Need for an Integrated Research Perspective

Evidently neither biological nor social theories of aetiology are adequate alone. Feminist authors, in particular, increasingly argue in favour of an integrated and multifactorial approach to researching the menstrual cycle (eg- Assó, 1992; Ussher, 1992; Gise, 1988; Hamilton, et al., 1984; Dan, et al., 1980; Koeske, 1980; Parlee, 1980, 1982; Sommer, 1973). Hamilton, et al. (1984) purport that the most appropriate

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In the section entitled "The seduction of science" in her recent book, Gloria Steinem (1992) quotes Einstein who said that, "[i]t is the theory which decides what can be observed." Steinem goes on to observe that "even the most objective areas of education need always to be questioned; the more they present themselves as value-free, the more the need for questions" (pp. 131-132).

concept of PMS, etc. which fits in with current research findings is that it represents a physiologically mediated "alteration in responsivity", and that researchers will need to explore neuropharmacologic models that "acknowledge multi-regulatory mechanisms". Gise (1988) has described cyclical change in terms of predisposing, precipitating, and sustaining factors. These might include: predisposing- past history of PMS, postnatal depression, or sexual abuse, family history of mental illness or of alcoholism; precipitating- pregnancy and childbirth, stopping the pill, tubal ligation, hysterectomy; and sustaining- life style factors such as diet, smoking, alcohol, exercise, and stress (Gise, 1988). Ussher's (1992) model which includes such contributory factors as personality traits, perceptions and attributions of physiological arousal, social support, utilization of coping mechanisms, and politics and culture is reproduced in Figure 2.02. Sommer (1973) suggests that individual expectations about the menstrual cycle ought to be fitted into the larger social pattern of its role in relationships, in the interrelations of persons and institutions.

Most such models are little more than theoretical conceptions, and no author has proposed how one would actually test hypotheses using an integrated approach. The most complete theories centre around the notion of increased activation or arousability at particular phases of the cycle (Asso, 1992; Koeske, 1980; Parlee, 1980, 1982). Asso (1992) has recently delineated a model based on the idea that cyclical fluctuations in hormones mediate changes in both central nervous system, and autonomic nervous system arousal, called respectively energetic and tense arousal, after Thayer (1989). Within this model these two sorts of arousal interact to produce changes in behaviour, mood, pleasurable bodily sensations, perceptions of self and of problems, memories of past events, and assessment of the likelihood of future outcomes. Tense arousal may be raised premenstrually, while energetic arousal is low leading to an enhanced responsiveness to strong stimuli. Koeske (1980) found large individual differences in the mode of expressing this sensitivity in her survey of university students, and also that at mid-cycle there was discordance between moods and external stimuli, while premenstrually external events were strongly related to moods. The implication of this is that women may be able to distance themselves from the realities of their lives through most of the cycle, but not premenstrually.

It seems inevitable that previous one-factor-one-cause theories must give way to a more complex aetiology of cycle-related phenomena (Parlee, 1980). One potential theoretical framework which has not been explored is the relationship of biological rhythms and

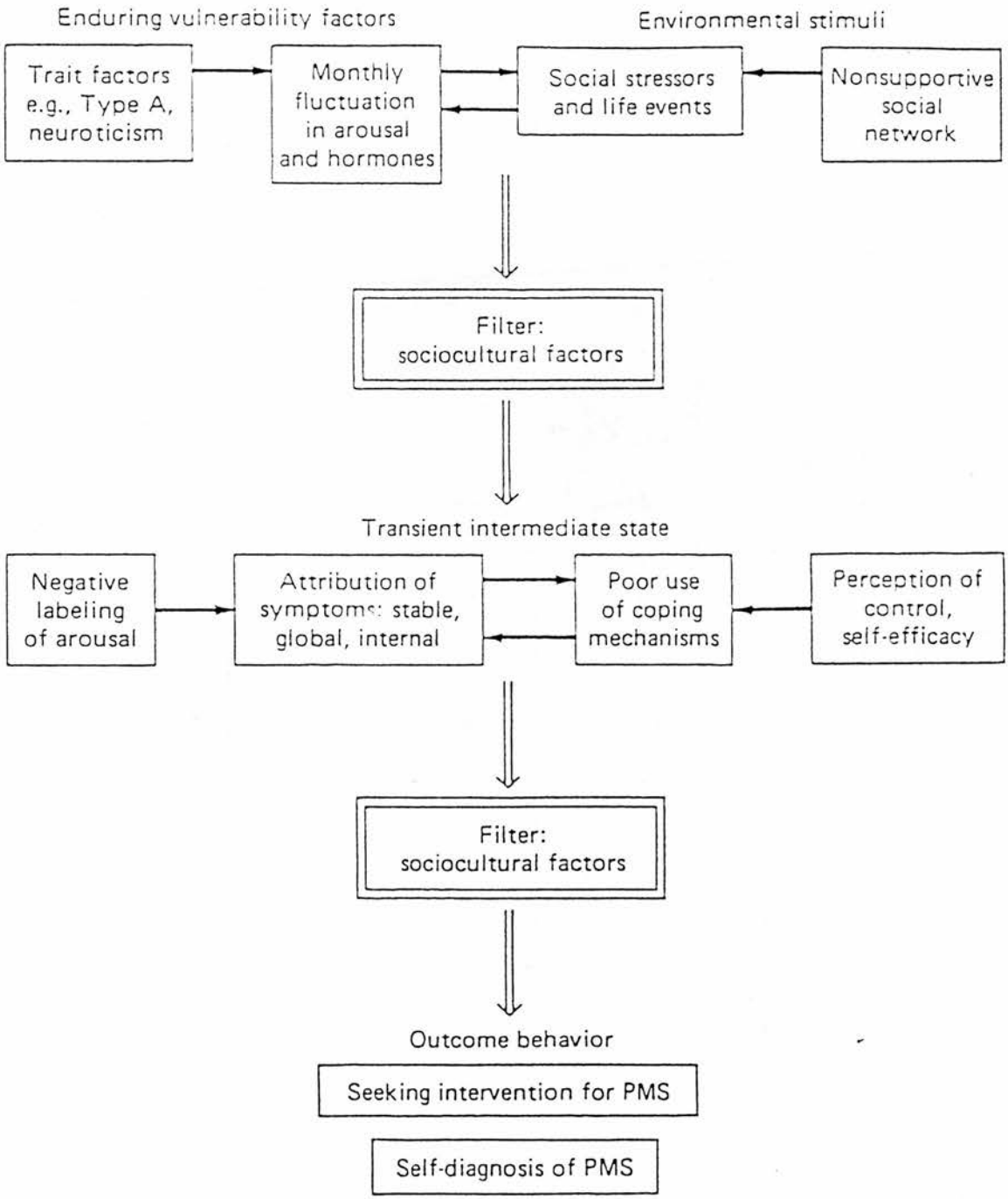

Figure 2.02 A multivariate model of the premenstrual syndrome from Ussher (1992), p.161.

well being to the menstrual cycle. This is a model which may account for biological and social contributions, for two way interactions between the internal and the external environment, and for individual variability.

2.7 A Novel Aetiological Theory for Cyclical Change: An Endogenous Biological Rhythm of Well Being

It has been noted that it is a fundamental error of experimental science to approach the organism and its responsiveness as constant phenomena because at different temporal stages the organism is a different biochemical entity (Halberg, 1980). The external environment is composed of a sequence of regularly changing conditions which exert selective pressure on organisms to which they must adapt in order to survive (Aschoff, 1980). The outcome of these selective pressures has been the evolution of biological rhythms. Although biological rhythms were first systematically studied in the 1700s, their genetic basis was only established in the mid 1930s, and a unified theory and disciplinary structure have only existed for about the last 50 years (Garfield, 1988).

Several authors have now proposed that there may be a mood cycle based in the brain which oscillates at about the same frequency as the menstrual cycle, and which constitutes a biological rhythm entrained to the steroid cycle (eg. DeVane, 1991; Reid, 1991; Walker & Bancroft, 1990; Rubinow, Hoban, Grover, Galloway, Roy-Byrne, Andersen & Merriam, 1988; Blumenthal & Nadelson, 1988; Hamilton, Parry & Blumenthal, 1988; Hamilton, et al., 1984). A variety of theoretical and indirect evidence exists in support of this idea, as does a small amount of recent experimental evidence. After a brief description of the background, definitions and basic properties of biological rhythms each kind of evidence will be considered in turn.

2.7.1 The Basic Properties of Endogenous Rhythms

The four major temporal cycles in the geophysical environment are the tides, the solar day, the lunar cycle, and the seasons (Aschoff, 1980, Rensing, 1972). However, biological rhythms have been documented which last for a fraction of a second or many years. The convention is to divide rhythms up into three classes by their duration: "ultradian" rhythms last for less than 24 hours, often a fraction of a day; "circadian" rhythms last for approximately one light/dark cycle or day and may be between 20 and 28 hours long; "infradian" rhythms last for more than 24 hours, usually many days

(Edlund, 1987; Moore-Ede, Sulzman & Fuller, 1982; Aschoff, 1981; Pittendrigh, 1981; Reinberg, 1974; Sollberger, 1965). Halberg introduced the term "circa" in 1959 to indicate the approximate nature of the rhythm with respect to a particular geophysical period. Thus there are also terms for weekly, fortnightly, monthly, and annual rhythms: respectively, "circaseptan", "circatidal", "circamensual" (also "circatrigintan"- about 30 days, "circasidereal" -about one tidal month of 27.3 days, and "circasynodic"- about one lunar month of 29.5 days), and "circannual" (Aschoff, 1981; Halberg, Halberg, Halberg & Halberg, 1980; Reinberg, 1974; Sollberger, 1965).

There are biological rhythms which correlate with all of these time periods. A biological rhythm is thus defined as the regular recurrence of an event at approximately regular intervals (Aschoff, 1981). Many biological rhythms have become built into the organism within a genetically determined physiological system of time measurement, and are therefore known as "endogenous". Such rhythms are responsive to signals from the external environment which give information about the cycles on which they were originally based, but are not dependent on these signals for their continued expression. In other words endogenous rhythms have the capacity to "freerun", or "persist for many periods without attenuation" when isolated from the synchronizing cycle (Aschoff, 1981; Pittendrigh, 1981). There are also "exogenous" rhythms which are driven by external fluctuations and will not persist in isolation from these cues. Some rhythms are only partially endogenous. Under freerunning conditions the partial rhythm is likely to continue for a short number of oscillations, with damped amplitude and perhaps lesser frequency, until eventual arhythmia (Sollberger, 1965).

Cues from the external environment (or in some cases from the internal environment of the organism) have been variously described as "*zeitgebers*"- or time-givers by Aschoff, "entraining agents" by Pittendrigh, and "synchronizers" by Halberg (Garfield, 1988). While each scientist originally proposed a slightly different definition, in practice all terms are now used interchangeably. The predominant zeitgeber for most organisms is solar illumination. Secondary signals are moonlight, temperature, barometric pressure, and electromagnetism (Sollberger, 1965). For humans an additional and important entraining influence is exerted by so-called "information zeitgebers", or social cues (Eastman, 1991; Edlund, 1987; Moore-Ede, et al., 1982). In the early 1960s individuals were kept in isolation in underground bunkers or caves for periods of a few weeks to many months. Several different experiments have revealed that the mean freerunning sleep-wake cycle in humans is approximately 25

hours. When these individuals were exposed to minimal "social information" like bells to indicate times to eat or wake up, they re-entrained to a 24 hour schedule (Moore-Ede, et al., 1982; Aschoff, 1980). The existence of circadian or diurnal rhythms is now well known in humans (eg.- Krieger & Hughes, 1980). Each species has a mean freerunning period length for each endogenous rhythm and individuals of the species have free-running period lengths that are normally distributed around the species mean (Aschoff, 1981).

Another alternative to a clearly endogenous rhythm, like circadian sleep-wake cycles, is the weak endogenous oscillator. Certain rhythms, at least in the circadian system, are known as dominant oscillators, while others are termed weak oscillators. This reflects how robustly they maintain their properties when freerunning, and thus their biological basis. One might imagine that it would be of greater selective utility for the organism to be able to anticipate some regular changes in the geophysical environment above others. Or in the case of rhythms which control the internal environment of the organism, it might be more important for that individual's survival to maintain some systems at the expense of others (Zucker, 1980). The parallel to this phenomenon in the external environment, is that there are both primary and secondary zeitgebers (Sollberger, 1965). The seasonal progression of solar day length is relatively invariate from year to year, yet the temperature pattern over the year is less predictable. Thus seasonal migration and reproductive behaviours are foremost determined by day-length and only secondarily by ambient temperature (Edlund, 1987). This way the animal cannot be readily tricked, or misread cues and behave in an unseasonable way, while it also provides the safeguard of secondary messages from the environment.

In humans there are two classes of circadian oscillator: 1) the dominant oscillator of body temperature, urine potassium excretion, cell division, plasma cortisol, REM sleep, etc. is robust and not easily disturbed, while 2) the weak oscillator of slow wave sleep, skin temperature, plasma growth hormone, and urine calcium excretion can readily deviate from a 24 hour cycle (Edlund, 1987; Groos, 1983; Moore-Ede, et al., 1982; Aschoff, 1980, 1981; Pittendrigh, 1981). Normally these two oscillators are "coupled" to one another, or operate in parallel, but under freerunning conditions the two systems tend to uncouple and freerun at their own characteristic frequencies after about one month (Moore-Ede et al., 1982). One consequence of the "weakness" of the sleep-wake cycle is that it is easier to phase-shift for therapeutic purposes than the circadian temperature rhythm.

The implication of this theory is that some rhythms will have greater functional significance than others, and therefore are more potent in the face of perceived disruptions. In this context, infradian rhythms may be seen as subordinate to circadian ones, and perhaps circadian to ultradian. There is, therefore, a hierarchy of rhythms within the individual with some that are essential for the proper function of others. Indeed, it would appear that some rhythms take their time cues from others, and that the manifestation of the "severity" of certain rhythms may depend on their phase relationship to more dominant rhythms (Aschoff 1981). These are sometimes known as "slave oscillations" (Pittendrigh, 1981).

The presence of two independent rhythm systems is supported by the physiological evidence for a brain based "biological clock". In 1972 two groups working independently isolated the pair of small bi-lateral nuclei now known as the suprachiasmatic nuclei (SCN) (see Moore-Ede et al., 1982). The SCN, in the anterior hypothalamus, are thought to be the seat of the "biological clock" in humans. If the SCN is damaged or removed, however, the circadian basal body temperature rhythm persists through some other mechanism (Aschoff, 1981). Moore-Ede et al. (1982) suggest that the pacemaker for the sleep-wake cycle is located in the SCN, while the temperature pacemaker is found elsewhere, possibly in the ventromedial hypothalamus. The SCN receive light cues directly from the environment via neuronal connections from the retina. The SCN also responds to melatonin manufactured by the pineal gland. The pineal in mammals is known as a "neuroendocrine transducer". Melatonin is synthesized in response to neuronal signals from the neurotransmitter, norepinephrine, and is closely linked with the sleep-wake cycle being high at night. The synthetic pathway is as follows: tryptophan to 5-hydroxytryptophan to serotonin to n-acetylserotonin to melatonin (Brzezinski & Wurtman, 1988). In humans, melatonin is thought to act exclusively on the SCN, and functions as an "internal zeitgeber" which signals the "biological clock" about day length (Cassone, 1990).

The timekeeping mechanism for longer term rhythms is not yet know. It used to be assumed that infradian rhythms were the sum of their component circadian rhythms, however some chronobiologists now believe that they must have an independent timekeeping mechanism (eg.-Menaker, 1974). Some examples of infradian rhythms are oestrous and menstrual cycles, and seasonal hibernation and aestivation, the 7 day rhythm of urinary 17-ketosteroid excretion, the 14 day rhythm of memory, the 21 day

rhythm of testosterone excretion in men, the monthly basal body temperature and steroid rhythms in women, and the 4 weekly rhythm of weight gain in men (LeConte, 1989; Edlund, 1987; Moore-Ede, et al., 1982; Aschoff, 1981; Luce, 1973). Such infradian rhythms might be expected to possess the same features of other circa-rhythms, namely, the ability to persist or freerun when the primary zeitgebers are held constant, and possess a regular mean phase length around which the freerunning phase of individuals will be distributed.

Certain terms and concepts are commonly used in biological rhythm research. The "cycle" or "rhythm" is any event which recurs at a predictable interval. The "period" is the amount of time it takes to complete one cycle. The "frequency" is the reciprocal of the period: eg. the frequency of sleep is once in 24 hours or 1/24. The "amplitude" of a rhythm is the amount that the cyclic parameter changes over the period. The period and the amplitude of rhythms may be variable, across and within individuals. The "phase" of a rhythm is the relationship of its peak or through to some other cycle in the body or an external marker. (Luce, 1973; Sollberger, 1965)

The concept of "phase" is very important in research because responsiveness to stimuli are often dependent on phase, and changes in phase or "shifts" may provide information about the mechanisms controlling a rhythm, and its degree of endogenicity. For example, Eastman (1991) found that there is a "phase response curve" (PRC) in individuals susceptibility to entrainment by bright light when attempting to compare the efficacy of gradual versus sudden phase changes in shift-work. Equally, Eastman & Miescke (1990) found that three quarters of volunteers could re-entrain to a 26 hour sleep-wake schedule while experiencing the conflicting zeitgebers of the 24 hour day, if they were exposed to bright light in the evenings. Yet they did not respond to morning light, or no light. There is also evidence that behaviourally arousing events have different potential to influence rhythm entrainment depending on where in the circadian cycle they occur. The degree of re-entrainment depends on both the timing and the duration of behavioural stimuli. For example, a 10km run in the early morning phase shifts the body temperature peak two hours earlier, while an early evening run does not alter body temperature (Mrosovsky, Reebs, Honrado & Salmon, 1989).

2.7.2 Evidence for Sex Related Differences in Biological Rhythms Particularly in Relation to Well Being

While the menstrual cycle is often cited as a long term biological rhythm, and authors proposing multifactorial causes for cycle-related change suggest that the relationship with circadian rhythms ought to be explored (eg- Reid, 1991; Hamilton, et al., 1984) little direct evidence for a biological rhythm of well being yet exists. However, there is evidence that certain affective disorders may have an endogenous rhythm component, namely depression, and seasonal affective disorder (SAD). Given that both of these are more common in women, it is possible that they may interact in some way with the hormonal changes that are unique to women.

SAD is an affective disorder with a clear temporal aspect. It takes the form of marked depression during the winter with increased appetite, increased sleep, carbohydrate craving and lethargy which resolves, or may turn to hypomania, during the light days of summer. SAD occurs mainly in women, and is effectively treated by bright full spectrum light administered for two hours in the morning and two hours in the evening, alternated with washout periods without light (Edlund, 1987). The hypothesized effect is to stimulate pineal melatonin secretion. SAD is not generally linked with a "neuroanatomical abnormality", however, recently a 45 year old woman developed recurrent winter depression and summer hypomania after an arterio-venous accident which caused damage to the right fronto-temporal region of her brain. The site of her lesion is consistent with that of patients with accident induced mania, and also with the idea that bipolar affective disorder may be associated with abnormality in the deep fronto-temporal region of the right side of the brain (Hunt & Silverstone, 1990).

Mania and depression have been known to be seasonal since ancient time. Depression shows a bimodal peak in spring and late autumn which may be related to circadian phase shifts induced by changes in daily photoperiod (Wehr, Wirz-Justice & Goodwin, 1979). It has also been know for about a century that sleep deprivation elevates mood in depressives. Much of the research relating biological rhythms to depression has been carried out at the National Institute of Mental Health in the United States by Wehr and colleagues. They have observed that a proportion of depressives have circadian rhythms of less than 24 hours, and thus possess sleep patterns in which the circadian rhythm of temperature and REM sleep, etc. are shifted 1 to 3 hours earlier (i.e.- "phase advanced") relative to normals (Edlund, 1987). This phenomena is marked in manic-

depressives, and there are many changes in circadian organization when they switch from mania to depression or vice-versa (Groos, 1983). So in order to compensate for the distorted phase relationship of internal rhythms, sleep can be phase advanced, or deprived altogether. Depression remits after sleep disruption, but only for about two weeks, a duration which is similar to the time it takes to restore circadian phase relationships after transatlantic air travel (Wehr, et al., 1979).

Evidence that circadian dysregulation does exist comes from sleep polygraph differences between depressed people and controls. Normally REM sleep dominates the latter half of the sleep period, but depressed individuals showed REM sleep within 40 to 50 versus 65 to 80 minutes of falling asleep. They also had less delta sleep and more REMs per minute than normals (Gillin & Borbély, 1985). These changes in sleep architecture are similar to those which naturally occur with increasing age. Interestingly, the incidence of depression increases with age, as may PMS. The tendency to experience internal desynchronization has also been linked to certain personality factors (Lunel, 1974). What is responsible for internal desynchronization is not entirely clear since some research finds no major alteration in melatonin function in depressives (Jimerson, Lynch, Post, Wurtman & Bunney, 1977).

It has been proposed that loss of social zeitgebers in the form of people, demands, or tasks that set the biological clock may contribute to the onset of a major depressive episode in vulnerable individuals. Life events occur which disturb social rhythms which in turn upset the stability of biological rhythms causing somatic and psychological symptoms. Some potential intervening variables are coping, social support, gender, and personality (Ehlers, Frank & Kupfer, 1988). It is also suggested that vulnerability to depression may be related to the quality of parental care received in infancy (Finklestein, 1989), which is responsible for establishing the pattern of and susceptibility to social entrainment of biological rhythms (Luce, 1973).

Further support for the notion of rhythm desynchronization in affective disorder comes from evidence that psychotropic antidepressant drugs may work by altering circadian phase positions and frequencies (Wirz-Justice & Wehr, 1983). The neurotransmitters serotonin, epinephrine, dopamine, the endorphins, and many of their metabolites which are involved in circadian time keeping, have circadian patterns of release themselves. All of the neurotransmitters and brain amines so far studied are phase-delayed by the tricyclic antidepressants. Lithium, which is used to treat a variety of "cyclic disorders"

including manic-depression, cyclic migraine, periodic hypersomnia, and periodic catatonia, also phase delays important rhythms such as calcium and magnesium release. Thus these drugs appear to exert their effect by correcting the phase advance of the dominant human oscillator in relation to the sleep-wake cycle (Edlund, 1987; Wirz-Justice & Wehr, 1983). It is not clear whether circadian phase disruption is aetiologic in mood disorder or an epiphenomenon (Edlund, 1987; Gillin & Borbély, 1985).

It is not evident that there are sex differences in the efficacy of psychotropic drugs or variable efficacy in relation to the menstrual cycle, however there is twice as much depression in women of reproductive age as men (Parry, 1989). Edlund (1987) includes PMS amongst "diseases that clearly possess desynchronization of physiological rhythms". Curiously, oestradiol and testosterone are two of a very few substances which have the power to alter circadian phase or rhythm frequency (Wirz-Justice & Wehr, 1983). It is probably not a coincidence that the site of the "biological clock", the hypothalamus, is also the endocrine "command centre" of reproductive function in women.

So efficient is biological timekeeping that humans can estimate short intervals of clock time (objective time) with great accuracy. Distortions of subjective time, that is the sensation of how quickly or slowly time "seems" to be passing are much more common than of objective time. Gross distortions in the ability to estimate objective time do occur in acute mental illness and during fever, while a common feature of depressive illness is that the future is (subjectively) "blocked off". Objective time estimation is linked to body temperature, and metabolic rate which may help to account for differences in subjective time experience in children versus adults. Given that women experience a regular shift in body temperature over the menstrual cycle it is not surprising that objective time estimation is more variable in women than in men (Edlund, 1987).

Another sex difference in biological rhythms is in the rate of chromosomal damage. Women show a cycle-related change in the amount of cellular genetic damage: sister chromatid exchanges and chromosome aberrations. There is more damage during the periovulatory/oestrogenic phases than the progestagenic phases. The authors of this research suggest that the sex difference may be due to more misrepair or errors of chromosome exchange in rejoining under hormonal influences at the cellular/receptor level (D'Souza, Thomas & Das, 1988). The above discussion suggests that the

reproductive hormone cycle may dispose women to biological rhythm disruption and to associated mood change.

2.7.3 The Interrelation of The Menstrual Cycle and Environment: Evidence for an Endogenous Infradian Rhythm of Well Being

The term "circamensual" testifies to the fact that the menstrual cycle is implicitly considered a biological rhythm. It certainly has the power to freerun without reinforcement from the external environment. And like other endogenous rhythms there is evidence that its length and other properties, such as the incidence of ovulation can be influenced by zeitgebers in the external environment.

2.7.3.1 Seasonal variation in reproductive rhythms in humans

Both male and female reproduction may be influenced by photoperiodic zeitgebers. Spermatogenesis in men has a seasonal pattern, with highest sperm counts in winter and spring, and lowest ones in summer (Politoff, Birkhauser, Almendral & Zorn, 1989). The evidence for an annual, light mediated cycle in the timing of human menarche has been reviewed by Reinberg (1974). Several studies show that there is a late autumn/early winter peak in menarche of about 30% (December to February) with a secondary peak of about 18% in summer (June to August). Further the occurrence of temporary amenorrhea (cycle of greater than 57 days) is twice as likely to occur during July and August than in any other two months of the year. It has been observed that menarche occurs earlier in prematurely born girls with impaired vision compared to controls, particularly if light perception is also lacking. Women kept in isolation without light cues show a free running circadian period of more than 24 hours, but "a circamensual spectral component" of body temperature shortens by about 3 days to 25.9 days on average, as does menstrual cycle length (Reinberg, 1974). Reinberg (1974) suggests that light may inhibit, or darkness stimulate, the human ovary, and that changes in day length over the year may act as a synchronizer. A circatrigintan temperature rhythm has also been observed in a male not exposed to any woman's menstrual cycle, and in premenarcheal girls (Halberg, et al., 1980).

In a study of 38,000 woman years of data reported by Hamilton & Alagna (1988) a tendency was found for cycles to be longer in the winter and shorter in the summer. Hamilton & Alagna (1988) report a similar pattern in their PMS clinic attenders which

they believe may account for cycle to cycle variability in PMS. They link long cycles to greater symptom severity, and note that more than 75% of women with SAD also report PMS. There is a marked temporal structure within the menstrual cycle itself. The LH surge seems to occur at a regular time of day from cycle to cycle (Dye, 1992; van Vugt , 1990). Women being monitored for spontaneous LH surges for oocyte recovery in IVF showed 42.5% of LH surges between 1:30am and 4:30am. The highest percentage of LH surges occurs in the early morning during the summer, autumn, and winter, but are 12 hours later in the spring (van Vugt , 1990).

The timing of labour and natural birth is no less precisely timed. The circadian peak in birth time estimated from over two million births is about 4am. The timing of still birth on the other hand differs from natural birth by about 12 hours, peaking at 5pm (Reinberg, 1974). Seasonal cycles in birth rate have been calculated from over 100 years of data from North American Eskimos. Births peak in March and are fewest in June, implying that conception actually peaks in June (van Vugt, 1990). Van Vugt (1990) argues that the lack of direct evidence for seasonal, photoperiod mediated reproduction in humans may be due to a loss of ability to respond to environmental cues due to our "artificial" environment. For example, monkeys reared indoors are unable to respond to photoperiodic cues once exposed to them.

Social cues may be of greater importance to people. Rossi (1980) has prospectively monitored mood cycles over the social week, and found that while men show greater weekly variation in mood than women, there is a reinforcing effect between mood response to the social week and menstrual cycle when they are synchronized. Regular weekly phase shifts in the sleep wake cycle also exist which are reentrained by alarm clock use (Binkley, Tome & Mosher, 1989). However, the sensitivity of some individuals to light cues may be underestimated. Melatonin levels do vary over the menstrual cycle, but the evidence for the timing of peak level is contradictory. Nevertheless, responsiveness to light cues may vary over the cycle. OC users have higher 24 hour melatonin profiles than non-users, thus there seems to be a positive relationship between melatonin and progesterone (Brzezinski & Wurtman, 1988). Inter-individual differences in cycle length may reflect variable sensitivity to light via melatonin (Asso, 1983). It is suggested that melatonin may influence ovarian function directly. Two possible modes of action are that melatonin modulates steroid synthesis by affecting enzyme systems in the follicular granulosa cells, or that it inhibits follicular proliferation (Brzezinski & Wurtman, 1988). The possibility of a direct effect of

internal synchronizers on the ovary might help to explain the effects of light, social interaction, and stress on the cycle which are reported in the next section.

2.7.3.2 The internal and external environments as modulators of cycle events

It was suggested in section 2.2.1.2 above that living circumstances can influence the incidence of ovulation (Metcalf & Mackenzie, 1980). There is an increasing body of evidence that social contact between women, social contact between women and men, and psychological and nutritional stress may all influence cycle events.

The oestrous cycle of rats and mice has been observed to alter in a number of ways in response to "social contact" with conspecifics. Female mice living in overcrowded cages are anoestrous, but if a male is introduced all the females come into oestrous synchronously. This is known as the Whitten Effect, and the proposed mechanism is that pheromones in the male's urine causes a drop in progesterone and an increase in gonadotrophin pulsatility. The Lee-Boot Effect refers to the higher than normal rate of pseudopregnancy in groups of 4 to 8 female mice housed together. Again the proposed mechanism is pheromones which increase FSH and prolactin stimulating the corpus luteum to secrete high levels of progesterone. The exposure of a recently mated mouse to a strange male results in frequent pregnancy failure via the introduction of cycling and an LH surge in the Bruce Effect. The Vandenberg Effect refers to the ability of some substance in male urine to advance sexual development in prepubertal female mice. (van Vugt, 1990; Campbell & Turek, 1981; McClintock, 1971).

Some of these effects have corollaries in humans. The effect of social contact on the menstrual cycle can be divided into the effect that women have on other women, which seems to be to promote menstrual synchrony, and the effect that men have on women, which is to ensure ovulation. McClintock (1983) has reviewed the evidence for pheromonal regulation of the ovarian cycle, and proposed a "coupled oscillator" model to explain how social contact mediated through pheromones influences the cycle. In short, follicular odours shorten the cycle while ovulation phase odours lengthen it. The coupled oscillator implies the presence of both phase advance and phase delay mechanisms which have differential effects depending on the cycle phase of the signaller in relation to the recipient. Menstrual cycle synchrony for example arises when the oscillators of different individuals are coupled or mutually entrained. Graham (1991) suggests that it is the hormonal events of the follicular phase which determine

synchrony in rodents and in humans. Thus similar cycle lengths reflect sychronization of the events leading up to ovulation. If this is so, then studies of menstrual synchrony should only include women who are ovulating, and should assess the timing of ovulation rather than the timing of menstruation. Graham proposes that discrepancies in the synchrony literature may be due to the fact that the research to date has focused on the timing of menstruation rather than of ovulation.

Rhythm coupling depends on the quality of social communication between individuals. Grooming in mice increases the effectiveness of chemosignals, and in humans it is evident that sharing the same physical environment is not enough to cause menstrual synchrony or induce ovulation. There is now a good deal of evidence that the menstrual cycle lengths and timing of menstrual onsets of women in close social contact like close friends and coworkers tend to converge (Graham, 1991). While there have been some negative findings and criticisms that synchrony may be no more than a tendency for the menstrual onsets of cycles of different lengths to randomly overlap one another (eg- Wilson, Kiefhaber & Gravel, 1991; Wilson, 1987) the bulk of evidence favours synchrony in a proportion of women (eg- Graham, 1991; Preti, Cutler, Garcia, Huggins & Lawley, 1986; Jarett, 1984; Quadango, Shubeita, Deck & Francoeur, 1981; Graham & McGrew, 1980; McClintock, 1971, 1983).

Menstrual synchrony has been documented in women at all-female colleges, women in co-educational colleges, co-workers and resident nurses (Graham, 1991) and may occur in small groups of women as well as pairs (Quadango, et al., 1981). Synchrony is rarely perfect, but an increase of a factor of two over the random level of synchrony is common. Between 17 and 31% of women fail to synchronize (McClintock, 1983). Most studies have shown that synchrony takes 3 to 4 cycles to develop (Graham, 1991; McClintock, 1983). Volatile fatty acid levels in vaginal secretions vary over the menstrual cycle with higher lactic acid concentrations at ovulation (Preti & Huggins, 1975). Olfactory sensitivity fluctuates over the menstrual cycle, with heightened sense of smell around ovulation (Asso, 1983). This indirectly supports the notion of a pheromonal mechanism.

A number of factors influence the likelihood of synchrony. The relationship between women needs to be emotionally close or interdependent, and they may have to spend more than a threshold amount of time together. Longer bleeds and the use of towels instead of tampons seems to be associated with greater synchrony. Women with

regular cycles may be more likely to "drive" women with irregular cycles. Personality variables may influence synchrony. Close friends with similar neuroticism scores on the EPI tend to show greater synchrony. In somewhat contradictory findings it has been shown that women who do not tend to "affiliate" with others, as well as women who have a high need for "social recognition" by others are more likely to synchronize with their college roommates. There is also some evidence that women who are highly stressed are not as likely to show menstrual synchrony, perhaps because they are refractory to signals from others. (Graham, 1991; Jarett, 1984).

Male-female contact seems to have a different effect on the cycle than female-female contact. Phylogenetic evidence supports the notion that humans may have the potential for reflex ovulation. Penile spines are always present in genera which ovulate reflexly, with the exception of certain primates species. Several species of primate including gibbons, orangutans, and chimps have penile spines, yet they are not reflex ovulators. However, primates are descendent from insectivores which have penile spines, and reflex ovulate. Laproscopic investigations have shown that conceptions can occur at any phase of the menstrual cycle and that the ovary may have the potential for ovulation at times other than midcycle. Clark & Zarrow (1978) cite reports that conception can result from rape at any phase of the cycle, possibly due to "the intensity of coitus". There is evidence from both non-human primates and humans that the incidence of ovulation in females who are isolated from males is low. For example, isolated female rhesus monkeys only ovulate 50% of the time (Clark & Zarrow, 1978), and the incidence of secondary amenorrhea in girls at boarding schools, convents, military academies, and drug rehabilitation centres ranges from 22 to 83%, far higher than in the normal population (Yamamora & Reid, 1990).

Winnifred Cutler and colleagues have published a large number of studies which suggest that regular sexual contact with a man "normalizes" a woman's cycle length and promotes presumptivley fertile basal body temperature rhythms. In one study of 94 gynaecologically mature undergraduates weekly coitus was associated with 29.5±3 day cycle lengths, while celibate women or those having sporadic sexual contact had more long or short cycles which are less likely to be ovulatory (Cutler, Preti, Huggins, Erickson & Garcia, 1985). Masturbation to orgasm was not associated with regular cycle lengths, while either coitus or genital stimulation by a male was. Ninety per cent of women having weekly coitus had apparently fertile basal body temperature rhythms, while only 55% of women having sporadic coitus, and 44% of celibate women did so.

In a later study regular coitus was shown to be related to significantly higher oestradiol levels during the luteal phase (Cutler, Garcia, Huggins & Preti, 1986a). Other studies have shown that sexual intercourse may not be necessary for fertility, as exposure to the axillary secretions of men[9] or spending two or more nights a month with a man will also promote fertile cycles (Veith, Buck, Getzlaf, Dalfsen & Slade, 1983; Cutler, Preti, Krieger, Huggins, Garcia & Lawley, 1986b).

Infertile women have been shown to have a significantly later age at first coitus, and more short luteal phases. The authors propose that luteal phase intercourse may play an important role in maintaining luteal function (Cutler, Garcia & Krieger, 1979a; Cutler, Garcia & Krieger, 1979b; Cutler, Garcia & Krieger, 1980). It seems that coitus may also influence male fertility. In an anonymous single case study, a male scientist recorded his beard growth while working in isolation on a remote island and related it to subsequent coital activity with his partner. While alone beard growth was slight, but one day before reunion with his partner it accelerated greatly, and remained high until two days after coitus. The importance of these findings are 1) that coitus can influence beard growth and therefore testosterone secretion, and 2) that accelerated growth precedes actual contact with the opposite sex (Anonymous, 1970). Thus, social cues appear to be powerful internal mediators of reproductive function.

Clearly social zeitgebers modulate the menstrual cycle. So too may lunar gravitation, nocturnal illumination, and psychophysiological stressors. There is a correlational relationship between phase of the lunar cycle and phase of the menstrual cycle. In several prospective studies, one of which was double-blind, a significant majority of women with approximately 29.5 day menstrual cycles (one synodic month) were observed to ovulate during the dark phase of the moon, and to begin to bleed during the light phase (Cutler, Schleidt, Friedmann, Preti & Stine, 1987; Friedmann, 1981; Cutler, 1980). Gravitational effects on the earth and its organisms are greatest during the new moon. Given that humans are composed mainly of water it is not unreasonable to imagine that they will be influenced by gravitational pull. Nocturnal low intensity bedside light shortened the cycle length of nine women from 45.7 days on average to 33.1 days (Lin, Krife, Parry & Berga, 1990), confirming Dewan's early finding that exposure to night-time illumination of a similar intensity to moonlight can shorten cycle length (Shuttle & Redgrove, 1986; Luce, 1973). This practice has probably been used

9
This research has been criticised on methodological grounds (Wilson, 1988) and the criticisms answered (Cutler, 1988).

for hundreds of years to "regularize" cycle length (Graham, 1991; Shuttle & Redgrove, 1986; McClintock, 1983; Cutler & Garcia, 1980).

Stress has long been known to disrupt the menstrual cycle. "War amenorrhea" refers to the frequent loss of menstrual cycling during wartime. In internment camps in Manila 23% of nurses and 15% of civilians developed amenorrhea before any nutritional effect could have occurred. Twenty-five percent of women in concentration camps who were not threatened with extermination were amenorrheoic versus 54% who were threatened. The extreme emotional shock of aerial bombardment can arrest endometrial development. (Yanamora & Reid, 1990; Sanders, 1984). There are case histories that acute psychological stress can even override the effects of exogenous hormone stimulation. In keeping with the coupled oscillator model of exogenous synchronizers and the menstrual cycle, environmental traumas cause different sorts of menstrual disruptions depending on whether they occur during the follicular or luteal phases (Sanders, 1984). Stress does not influence all individuals in the same way. If it did then all women in concentration camps would have been amenorrheoic. Some potential mediating factors are cognitive appraisal, behavioural adaptations, and the social and personal characteristics of the individual (Yanamora & Reid, 1990).

The circadian phase disruptions which long-haul flight attendants experience very often produce cycle irregularity, as does hospitalization for non-gynaecological surgery (McKeever & Galloway, 1984; Iglesias, Terres & Chavarria, 1980). Stress may also be nutritional or hypoxic. Both obesity and anorexia can result in cycle irregularities, and it is arguable that one objective of anorexia is to produce amenorrhea. Intense exercise may also alter the cycle. (For review of psychosomatic aspects of amenorrhea see Sanders, 1984).

There is thus considerable evidence that the menstrual cycle constitutes a long term infradian rhythm that is susceptible to the influence of the primary entraining agents in humans: photoperiodic and social cues. It also seems that the stability of the rhythm in the face of potential disruptions is mediated by the characteristics of the individual and her immediate environment.

2.7.3.3 Experimental evidence for an endogenous infradian rhythm of well being

What evidence is there for an infradian rhythm of well being which parallels the menstrual rhythm? Hamilton, et al. (1988) propose that the mood cycle is "periodically entrained" to the menstrual cycle, such that menstrual and affective symptoms may overlap for months or years and then dissociate, or symptoms occurring monthly may continue even after the cessation of ovarian functioning. It seems likely that the steroid cycle "entrains" the mood cycle to it, and that at times when the steroid cycle is disrupted or suspended the mood cycle will also loose entrainment. Metcalf, et al. (1991) note that after hysterectomy there seems to be a "loss of entrainment" of PMS symptoms with shifts in timing to phases other than the luteal phase. Such a mechanism might also explain the transient worsening of symptoms that occurs with the use of oestradiol patches or GnRH analogues (Mortola, et al., 1991; Watson, et al., 1989; Bancroft, et al., 1987b). DeVane (1991) posits that there may be a dose dependent relationship between cycling steroids and entrainment of the mood rhythm. This might help to explain why OC use often alters the nature of mood and other cycle-related symptoms but does not abolish them.

Rhythms of different frequencies may influence one another. It has been suggested that circadian rhythms gradually shift their phasing over the menstrual cycle, and that PMS-type symptoms arise from progressive phase desynchronization, or a sort of cumulative "jet-lag" effect (Dye, 1992; Parry, 1990; Parry, Rosenthal, Tamarkin &Wehr, 1987). In a case which seemed to encompass the interaction of menstrual, mood, and seasonal rhythms a woman experienced PMS only during the autumn and winter, but was symptom free in the spring and summer. She was effectively treated with bright light therapy as in SAD, and this effect was reversed by the administration of melatonin. The effect of the melatonin was then overcome by the administration of melatonin inhibitors: Propanadol, Atenolol, and ß-antagonists (Parry, et al., 1987). Maurizi (1988) suggests that normal melatonin rhythms may be antidepressant, while if the phase relationship of the melatonin rhythm and other circa-rhythms is disrupted it may promote depression. Women with PMS characterized by depression do not have the same abnormalities of sleep architecture as depressed patients, however they respond as well as, or better than, depressives to sleep deprivation. Eighty per cent of depressed PMS sufferers had no more depression for the remainder of the cycle after a night of sleep deprivation during the luteal phase (Parry, 1990). Parry concludes that "...[C]ircadian dysregulation, whether induced by lifestyle, environment, or the

reproductive system, may be a common pathogenetic factor in PMS and possibly in other cyclic mood disorders." (p.86, Parry, 1990)

The alternative to circadian dysregulation is that there is a genuinely infradian rhythm which manifests itself as a mood and physical cycle in harmony with menstruation. Only one study to date has explored this possibility. In an ingenious experiment Schmidt, Nieman, Grover, Muller, Merriam & Rubinow (1991) used the anti-progestin RU486 to curtail luteal function and advance menstruation in women with prospectively confirmed PMS. Three groups of seven women each were randomly allocated to one of three experimental treatments in a double-blind placebo design. The 21 women had prospectively confirmed cyclical symptoms in the luteal phase in at least two out of three baseline cycles. Group 1 had their cycles truncated with the administration of RU486 seven days after the LH surge, and placebo saline injections on days 6, 7, and 8 after the LH surge. The physiological outcome was luteolysis followed by vaginal bleeding within 72 hours, and normal ovulatory steroid profiles in the next cycle. Group 2 was also given RU486, but in a lower dose along with injections of hCG in order to produce bleeding, but preserve luteal function. The regime had the desired outcome, and these women continued to have luteal phase steroid profiles, and to have a second bleed at the end of the luteal phase 8 to 10 days after hCG was given. Group 3 was given a placebo tablet on day 7 and saline injections on days 6 to 8 after the LH surge. Their luteal function was not affected, and they did not bleed until the end of the normal luteal phase.

For the treatment period women completed daily 16-item self rated visual analogue scales, and a 21-item 6-point scale rating form. Daily ratings were analysed using analysis of variance for repeated measures. The seven days prior to the LH surge were compared with seven days beginning five days after the administration of RU486 or placebo. This was meant to compare the follicular and real or "would be" luteal phase. The authors found that neither mood nor somatic symptoms differed in timing or severity over the three groups. They conclude that: "[n]either blockadé of the action of progesterone alone nor the truncation of the luteal phase of the cycle altered the course or severity of the symptoms of PMS, and these symptoms developed and progressed during the hormonal conditions of the follicular phase." (p.1177, Schmidt, et al., 1991) They offer two potential explanations for why PMS symptoms occur with consistent period: 1) PMS is caused by hormonal changes, or by abnormal sensitivity to hormone changes. Thus, symptoms could be triggered by some hormonal event which occurs

earlier in the cycle than the luteal phase which would explain "follicular phase" symptoms with RU486; 2) PMS symptoms are caused by a cyclic mood disorder which is synchronized with the menstrual cycle wherein the steroid cycle acts as the main zeitgeber, but are not directly caused by it. These findings are consistent with the existence of an infradian oscillator, as opposed to progressive, hormone mediated circadian dysregulation.

RU486 provides a useful experimental tool for exploring the aetiology of cyclical change, however, it does not lend itself to easy and repeated cycle phase manipulation. A readily available, and safe alternative method is to use oral contraceptives to alter cycle length, or cycle phase. Although the pill cycle is hormonally distinct from the menstrual cycle, there is ample evidence that changes in well being are similar under the two conditions. The pill cycle offers great scope to explore the consequences of altering the timing of steroid withdrawal and bleeding on the purported infradian well being oscillator.

A few studies have examined the effects of extending pill taking in order to postpone withdrawal bleeding. These studies have been particularly interested in assessing the acceptability of contraceptive regimes which induce amenorrhea, or reduce the frequency of bleeding, but none has systematically investigated the relationship between steroid cycle length and well being. The four studies conducted to date are summarized in Table 2.04. In the region of 80 to 90% of women found extended pill taking acceptable, although breakthrough bleeding was common. Bleeding occurred least on the high dose pill Minilyn, and the gestodene containing 30μg pill Minulet. Side effects of the sort often reported during the conventional pill cycle were indicated, and in only one study was PMS mentioned. Loudon, Foxwell, Potts, Guild & Short (1977) indicated that many women noted that they had a reduction in "menstrual and premenstrual symptoms", but they do not elaborate on the nature of the changes. In spite of no adverse medical consequences, the medical staff were more reluctant about extended pill taking than the volunteers.

The discrepant findings of these studies probably relates to a number of methodological problems including: 1) no control cycle to assess the baseline rate of breakthrough bleeding, 2) no separation of women starting the pill and women established on it, 3) no hormonal tracking, 4) no distinction between spotting and breakthrough bleeding, and no consistent definition of either, 5) different information to volunteers about what

Table 2.04 Studies of the Effects and Acceptability of Manipulating Oral Contraceptive Cycle Length

Study	Pill Type/s	Regime	Effect on Bleeding	Other 'Side Effects'	Acceptability
Loudon, Foxwell, Potts, Guild & Short (1977) n=196	Minilyn 50µg EE +2500µg LYN	84 days active+ 6 pill free days, repeated 4 times over 1 year	24% spotting in 'cycle'1 & 3% btb; of those remaining 4% spotting & 0% btb in 4th 'cycle'	dysmenorrhea 9%, weight gain (2kg+) 46%, headaches 11%, reduced menses related 'symptoms' 20%	82% of women were happy with the reduction in bleeding and other 'symptoms', Clinic staff were less accepting
Hamerlynck, Vollebregt, Doombos & Mutendam (1987) n=101; 37, 29 & 34 respectively	1) Microgynon 30µg EE +150µg LNG 2) Marvelon 30µg EE + 150µg DSG 3) Logynon 30-40µg EE + 50-125µg LNG	monophasics- 42 days active+ 7 pill free days triphasic- 21days+2x 3rd phase = 41 days active+ 7 pill free days	significant rise in btb and spotting after day 21 with more btb in triphasic takers, 55% of women had some bleeding in weeks 4-6 of continuous pill taking	breast tenderness, abdominal pain, headache, weight gain, and depression noted, but could not be attributed to pill type or regime, no incidences given	acceptability related to bleeding experience, 49% of women would favour bleeding every 3-6 months, 32% would like total amenorrhea, 29% of women with bleeding found the regime acceptable
de Voogd, (1991) n=105	Marvelon 30µg EE + 150µg DSG	42 days active+ 7 pill free days	btb and spotting not distinguished, 75% of women free of bleeding in weeks 4-6	no information given	women with btb were significantly less likely to accept the regime, though 87% overall said they would do so
Kornaat, Geerdink & Klitsie (1992) n=55	Minulet 30µg EE + 75µg GSD	42 days active+ 7 pill free days	96% had no btb, 81% had no btb or spotting	breast tenderness 7%, nausea 4%, bloating 4%, headache 2%, period type pain 2%	90% of respondents were satisfied with bleed postponement, and 4% were dissatisfied

Key: EE-ethinyloestradiol, LYN-lynestrenol, LNG-levonorgestrel, DSG-desogestrel, GSD-gestodene, btb- breakthrough bleeding.

to expect from manipulations, 6) no measure of the influence of women's attitudes on drop out rates or reported acceptability, and 7) biases in results due to the attrition of women who had bleeding or other difficulties.

2.8 Overall Conclusions and Strategies for This Research

A wide body of literature has been drawn upon in the above discussion, and a number of general, interrelated themes emerge. They may be summarized briefly as follows: A significant proportion of women experience emotional and physical fluctuations in their well being in close temporal relation to the menstrual cycle. The bulk of evidence suggests that both hormonal and social/psychological factors play a role in the aetiology of cyclical change. However, the relative contribution and the mechanism of each of these is not adequately understood, and multifactorial research and explanations are essential. The variability of the menstrual cycle itself, and of individual women's experience of it, presents a number of methodological problems for research. The experience of most pill takers is not markedly different from that of women having spontaneous menstrual cycles. However, the mode of action of OCs and the degree of ovarian suppression generated by low dose pills is not fully understood. There is increasing evidence to support the notion that the menstrual cycle and its sequelae form endogenous biological rhythms which are susceptible to the entraining influence of a variety of factors in the external and the internal environments.

The combined oral contraceptive pill presents a useful experimental model of the steroid hormone cycle in women which is potentially more tractable and less variant than the menstrual cycle. The possibility that persistent cycles of well being on the pill arise from residual ovarian function has not been explored. The possibility that endogenous hormonal change, even of a modest level, without ovulation can drive such changes needs to be explored. In addition to assessing the hormonal factors it is also essential to develop a broader understanding of women's beliefs about menstrual bleeding, the pill, and cyclical changes. Such examinations might help to clarify the mechanisms by which beliefs held by society and individuals can influence subjective experience. Finally the inadequacy of previous unitary theories for the aetiology of cyclical change demand a novel approach. The existence of an infradian rhythm of well being which is linked to the steroid cycle can be readily tested by manipulating the purported steroid zeitgeber, and exposing the rhythm to freerunning conditions. Should such a rhythm exist it might account for much of the inconsistency of previous findings.

Four investigations are reported in the subsequent four chapters which address these research questions in turn. This research is not concerned with the question of PMS as such, but with the fundamental exploration of the nature of cyclical changes in samples of women from the normal population. Methodological issues differ widely in the various investigations due to diverse disciplinary underpinnings. Therefore, questions of methodology are addressed as appropriate in each chapter, and not concentrated in one chapter on methods and materials. There was obviously overlap in the techniques used to assess endogenous steroids and subjective state, therefore, the methodology is described the first time the technique appears and not described subsequently unless some modification has been made in a different investigation.

Chapter 3 Ovarian function during low dose pill cycles and its association with variations in subjective state

3.1 Introduction

Two of the important facts which were established in the previous chapter were: 1) that the ovary continues to function at a reduced level during modern low dose OC use, and 2) that women who use OCs experience cycle-related changes in subjective state in a similar manner to women having spontaneous menstrual cycles. One possible aetiological explanation for the persistence of cyclical oscillations in well being for a proportion of women during the hormonally distinct conditions of the pill cycle may be residual ovarian function. An investigation of the previously unexplored relationship between these two phenomena is described in this chapter.

3.2 Aims of Study

This study aimed to assess : 1) the degree of folliculogenesis which occurs in long term pill takers; 2) the degree of cyclical variation in subjective state which occurs; 3) whether monophasic and triphasic takers differ with respect to either of these factors and ; 4) whether there is any association between the timing and severity of fluctuations in well being, and the degree and timing of ovarian hormone output. In addition to these primary aims, the relationship between retrospective PMS reporting and personality was explored.

3.3 Study Design

The design of the study is represented schematically in Figure 3.01. Volunteers well established on either a monophasic or a triphasic preparation were monitored over a period of ten weeks, or two and a half pill cycles. During this time each woman kept a daily record of her physical and emotional well being, and collected first morning urine samples for hormone determination. Daily monitoring began on day fifteen of the pill cycle, the beginning of the third week of pills. This timing was chosen in order to include three pill free intervals (pfi) as the weeks surrounding the pfi are hypothetically the time when hormonal events, as well as changes in subjective state, are likely to be concentrated. Volunteers were enrolled in the study at a structured questionnaire based

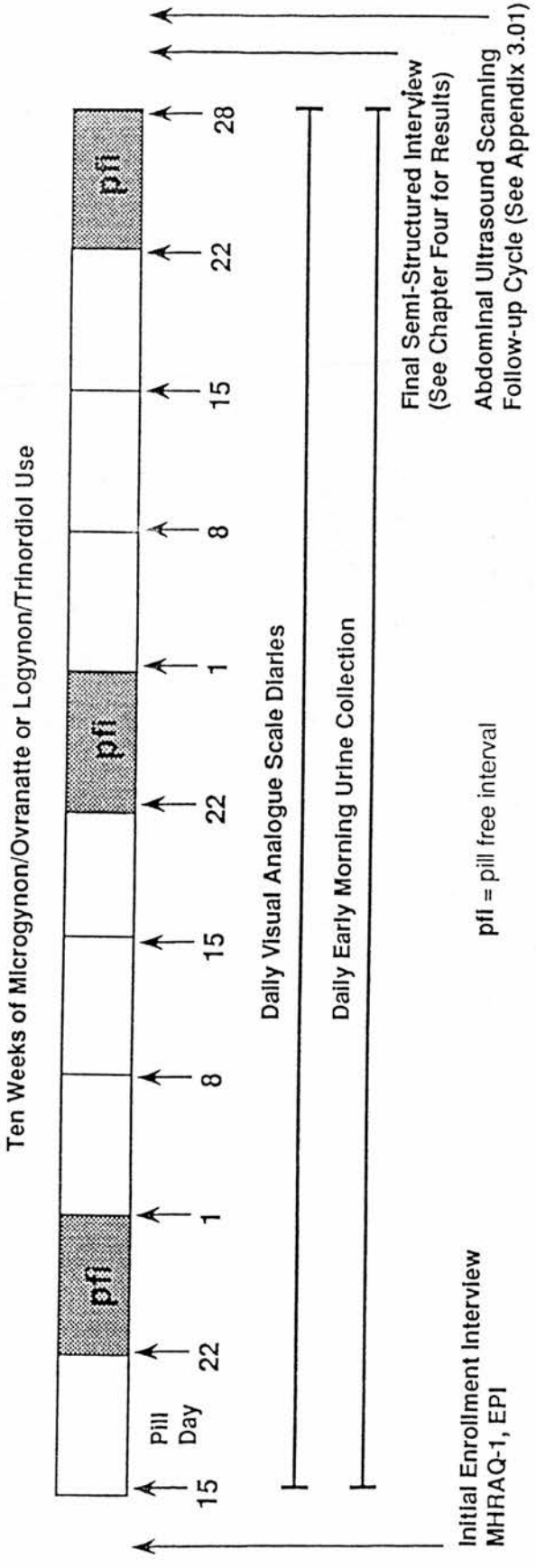

Figure 3.01 Study design.

interview. After the ten weeks of monitoring, a semi-structured interview was carried out concerning volunteers' attitudes towards and beliefs about menstruation, contraception, and other aspects of reproduction and gender. The findings of this interview are reported in Chapter Four. A subgroup of women were monitored over one pill cycle using abdominal ultrasound. The methodology and findings of this subsidiary investigation are reported in Appendix 3.01.

The two formulations of OC targeted for examination in this study were Microgynon®/Ovranette® and Logynon®/Trinordiol®. The comparative dosage of synthetic steroids in these formulations are given in Table 2.03, and their other properties are discussed in section 2.1.2.1. These two formulations were chosen because they are 'low dose' (<35μg per day), are widely prescribed, and contain analogous steroids, so they may be sensibly compared. This triphasic formulation is also the only one in which both oestrogen and progestagen doses vary over the cycle. And finally, these pill types have been quite widely used in investigations both of folliculogenesis (e.g.- Molloy et al., 1985; Smith et al., 1986; van der Spuy et al, 1990), and of subjective state changes over the pill cycle (e.g.- Bancroft et al., 1987a; Walker and Bancroft, 1990; Walker, 1987). Figure 3.02 schematically compares the synthetic hormone regimes with the urinary steroid profiles of the 'normal' menstrual cycle. Note that the 'shapes' of the triphasic profiles roughly approximate the profiles of endogenous steroid. The profiles of oestrone-3-glucuronide and pregnanediol-3-glucuronide shown here are derived from normative data for the In-house urinary steroid ELISA's for these hormones.

Ethical approval for this study was obtained in writing from the Paediatric/Reproductive Medicine Ethics Sub-Committee based in the Simpson Memorial Maternity Pavilion of the Royal Infirmary of Edinburgh. The Committee did not request any changes to the protocol as submitted, and approval was granted in September, 1988.

3.4 Selection Criteria and Recruitment Procedure

Individuals were recruited from the Lothian Health Board, Family Planning and Well Woman Services Dean Terrace Centre (FPC) in Edinburgh. This was thought to be an appropriate location from which to draw a 'normative' sample of hormonally contracepting women as more than 60% of Clinic attenders use the pill. Permission to recruit from the FPC was obtained in advance from the then Director, Dr. Nancy

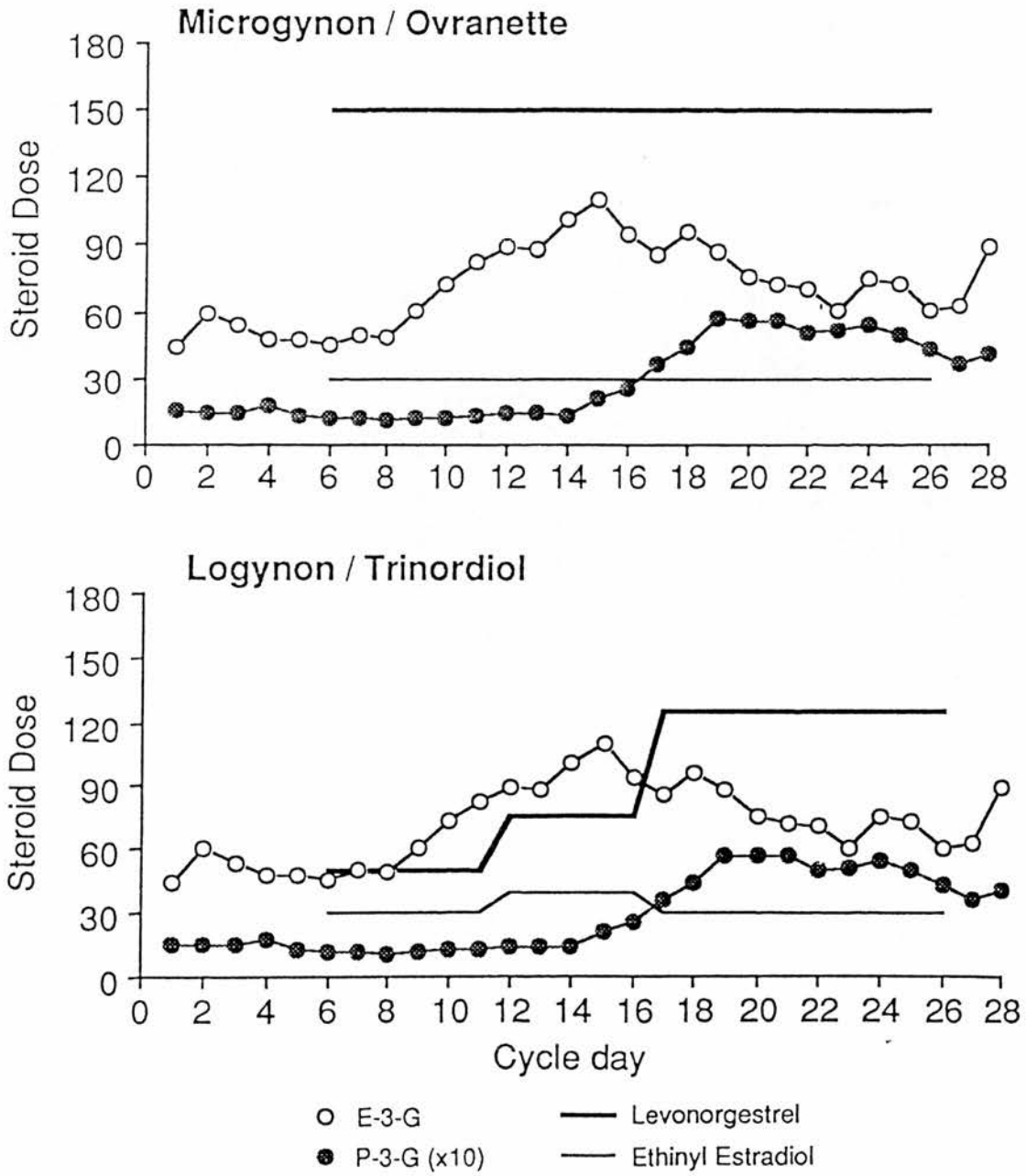

Figure 3.02 Schematic graph of the levels of synthetic steroids in the monophasic and triphasic combined pills used in the folliculogenesis study in comparison to the levels of endogenous urinary steroids during the normal menstrual cycle.

Loudon. Further discussion of the characteristics of the FPC population is contained in Chapter Four.

A large poster was placed in the Clinic waiting room that summarized the selection criteria: PARTICIPANTS NEEDED: DO YOU TAKE THE PILL? DO YOU TAKE ONE OF THESE FOUR BRANDS? (Microgynon, Ovranette, Logynon, or Trinordiol) HAVE YOU TAKEN THIS SAME BRAND OF PILL FOR SIX MONTHS OR LONGER? ARE YOU AGED BETWEEN 20 and 35? IF YOU HAVE ANSWERED "YES" TO ALL THESE QUESTIONS, YOU MAY BE ABLE TO HELP US BY PARTICIPATING IN A STUDY ON THIS SUBJECT. PLEASE TAKE A LEAFLET FROM THE POCKET BELOW TO LEARN MORE ABOUT OUR INVESTIGATION, AND THE ROLE YOU MIGHT BE ABLE TO PLAY IN IT.

The age criterion was based on the fact that women younger than twenty and older than thirty-five may not ovulate as frequently as women in the 20 to 35 year age range who are likely to ovulate about 90% of the time if they are not using hormonal contraception (Metcalf & MacKenzie, 1980). This study was concerned with monitoring ovarian function, hence women with maximum ovulatory 'potential' were selected. Each woman had to have taken one of the four brands of contraceptive mentioned above for at least six months, be healthy, not taking psychotrophic drugs, and able to meet all the study demands, eg.- possess a freezer to store urine samples. Women were not selected according to whether or not they reported cycle-related fluctuation in well being. Recruiting leaflets which explained the purpose of the study more fully were held in a pocket beneath the poster (see Appendix 3.02).

In addition to the poster, I attended a number of daytime and evening family planning sessions at the FPC over the course of several weeks during September and October, 1988 to approach women myself. If I was not in the Clinic, women who had an interest in the study were requested to hand their name and address in to the staff at reception. I attended clinics until I had secured a commitment from ten women using each formulation. It was not possible to keep track of the exact number of women who were approached to take part. At least ten women were asked for every one that was suitable and wished to volunteer. Women who dropped out of the study, or changed their minds after initial agreement were replaced so that the total would remain twenty. Each woman was approached before or immediately after she had seen the doctor. I briefly explained what the study would involve and ascertained whether or

not she met the selection criteria. If she was interested in taking part I offered her the information sheet to read (see Appendix 3.03), took her name and address, and if possible fixed a time for our initial appointment.

3.5 Methods of Assessment

Folliculogenesis and subjective state were measured in five ways. The status of the ovary was assessed by steroid hormone assay of first morning urine samples and by ultrasonography in a subset of women. Biographical data and measures of subjective state were collected using questionnaires, and daily self-reported diaries. Interviews employing discourse analysis techniques were used to gather qualitative information about women's reproductive attitudes. The sections below describe the measuring techniques in detail.

3.5.1 Initial Interview

The initial study interview took place approximately one week before each woman began daily recordings. Interviews were conducted by the author, in the woman's home, or at the Centre for Reproductive Biology, Edinburgh according to the volunteer's convenience. Each session took about one hour. The following schedule was adhered to in all cases.

I ensured that the woman had read and understood the Information Sheet (Appendix 3.03) describing the study requirements. I obtained her General Practitioner's address in order to let her/him know that her/his patient was taking part in the study. I then gave her the Menstrual Health and Reproductive Attitudes Questionnaire (MHRAQ-1) to complete. Although she filled in her responses herself, the questionnaire was completed interactively. She was free to ask for help, and I for elaboration at any time (which I noted). MHRAQ-1 generally took about 45 minutes to complete, and thus accounted for most of the hour. After she had completed the MHRAQ-1, I asked her to read the instructions for, and complete, the Eysenck Personality Inventory (EPI), Form A. She did this on her own, and it generally took about five minutes. Once both questionnaires had been filled out, I explained the method of urine collection, and how to complete the daily diaries.

3.5.1.1 Menstrual Health and Reproductive Attitudes Questionnaire - Version one (MHRAQ-1)

As it name suggests the Menstrual Health and Reproductive Attitude questionnaire used in this thesis was designed to elicit information about women's menstrual bleeding patterns, past bleeding experience, and cycle-related change, along with demographic information, history of pill use, and certain related attitudes. A copy of MHRAQ-1 is contained in Appendix 3.04.

All of the versions of the questionnaire used in this thesis were based on an instrument that was originally developed in Edinburgh in 1984 by Dr. John Bancroft's research team, called the Menstrual Health Questionnaire (MHQ). An early version of the MHQ was used to survey 7000 *Woman* magazine readers in 1985. The design and piloting of the questionnaire and the results of this survey are described in Bancroft & Warner (1987) and Warner & Bancroft (1990). The MHQ has been used in several other Edinburgh studies since 1984 (eg. Bancroft, et al., 1992; Warner et al., 1991; Walker, 1987), and has received a number of modifications over time.

Modifications have been a function of the research use to which it is being put. For example, the questionnaire was originally devised to measure the incidence and features of cycle-related change in physical and emotional well being, but was expanded to include questions about amount of menstrual bleeding and pain (Bancroft, et al., 1992). The MHQ is also routinely used at "booking" in the Premenstrual Syndrome Clinic at the Royal Infirmary of Edinburgh to provide information about change in cyclical well being and previous treatments used for PMS.

The first version of the Menstrual Health and Reproductive Attitudes Questionnaire, (MHRAQ-1) differs from the MHQ in three principle ways. Firstly, the language and questions have been modified to be appropriate to pill takers. Menstrual periods are referred to as "bleeds" to denote hormone withdrawal bleeds, and to avoid reinforcing the concept that a withdrawal bleed is equivalent to, or the same thing as a menstrual bleed. Further, questions have been added about pill taking history, beliefs about the benefits and risks of the pill, and about the pill's influence on bleed volume and the physical and emotional concomitants of the cycle.

The second major change is that questions have been added about women's menarcheal experience, and current beliefs and attitudes relating to vaginal bleeding. The content

and phrasing of these questions was developed through an assessment of prominent themes in the literature on attitudes, as reviewed in Chapter Two. The questions in the MHQ concerning treatments tried for heavy or painful bleeding and PMS were omitted from the MHRAQ-1, while questions relating to pregnancy experience and psychiatric history were retained. The MHRAQ-1 also differs from the MHQ in the manner in which women were questioned about their retrospective experience of cyclical changes. In the MHQ women were requested to describe the "symptoms and changes" that they experienced "before, during, and after" their *last period.* Volunteers, on the other hand, were asked to describe a summary view of their *"usual"* cyclical experience.

MHRAQ-1 was piloted in interactive interview sessions with three volunteers. The objective of this exercise was to establish whether or not questions were clear, meaningful and salient (face validity), to eliminate repetition, and to determine how long it would take to complete. The instrument was modified based on these sessions, and consultations with John Bancroft, Anne Walker, Pam Warner, and Lynn Williamson all of whom have used earlier versions of the MHQ in previous research projects.

3.5.1.2 Eysenck Personality Inventory (EPI)

Anastasi (1982) describes psychometric personality tests as "instruments for the measurement of emotional, motivational, interpersonal, and attitudinal characteristics, as distinguished from abilities" (p.497). The Eysenck Personality Inventory (EPI) is a widely used psychometric test designed to assess two different aspects of personality: extroversion and neuroticism. As indicated in Chapter Two, high neuroticism (N) scores on the EPI have been shown to correlate with the severity of reported PMS symptoms. The EPI has some shortcomings. The language is somewhat dated, and there is a slight gender bias: women tend to score higher on neuroticism and lower on extroversion than men. It arguably produces a fairly unrefined description of personality. However, it remains useful in a research setting since it is valid and takes far less time and expertise to administer than the other commonly used personality inventories (eg.- Minnesota Multiphasic and Cattell Personality Inventories). The completed forms were coded using the published scoring template, and scores were related to the normal population means (Eysenck & Eysenck, 1964).

3.5.2 The Daily Visual Analogue "Diary"

3.5.2.1 Content, instructions and coding

In a study relating well being to physiological change it is extremely important to have an appropriate means of measuring subjective state. As noted already, there is an on-going discourse in menstrual cycle research about the utility of retrospective versus prospective techniques for monitoring cycle-related change. It is now widely accepted that prospective monitoring is essential for methodologically rigourous research of phenomena associated with hormonal cycles. A variety of different formats have been used by the Edinburgh research group for self-rating scales. All of these take the form of a one page 'diary' on which volunteers or patients are required to rate themselves on a number of pre-formatted scales of commonly reported symptoms and changes associated with the menstrual cycle. For further description of diary development and validation see Sanders (1981) and Walker (1987).

Three forms of the daily diary were used in this thesis. The later two are described in Chapters Five and Six. The first diary, shown in Figure 3.03, was comprised of twenty-one (21) predefined unipolar 100mm visual analogue scales (VAS), and two (2) blank scales on which a woman could record other cyclical changes besides those mood and physical scales already designated. Seven one-page A-4 forms were stapled into weekly booklets.

The final composition of scales included in the diary was based on careful consideration of the frequently reported cycle-related changes in the research literature, discussions with the members of the Edinburgh group who have prior experience of daily diaries, and theoretical consideration of the nature of PMS and cyclical change. An effort was made to include positive as well as negative feelings. Thus there were six positive and seven negative mood variables, five physical variables which may be construed as being largely negative, and three scales relating to sexuality. All scales were demarcated with a '0' for 'the least you have ever felt this' and '10' for 'the most you have ever felt this'. Five scales were described by more than one adjective in order to help the woman "conceptualize" the mood. It was hoped that this approach would help to generate ideas whose meaning was consistent across women.

"Feeling sexually attractive" was intended as a barometer of sexual self image, but not necessarily of active sexuality. "Sexual interest" on the other hand was supposed to

CODE NO: ☐☐☐☐ DATE: ☐☐/☐☐/☐☐

Time of Waking ☐☐:☐☐ Time of Retiring ☐☐:☐☐
Caffeine Intake (No. cups coffee, tea, or Cola)
Smoking (No. cigarettes)

1) CHEERFUL AND HAPPY	0	10
2) DEPRESSED AND UNHAPPY	0	10
3) ENERGETIC AND ACTIVE	0	10
4) FATIGUED AND TIRED	0	10
5) CREATIVE	0	10
6) IRRITABLE	0	10
7) RELAXED	0	10
8) AGGRESSIVE	0	10
9) MOOD UP AND DOWN	0	10
10) TENSE AND ANXIOUS	0	10
11) FEELING GOOD ABOUT SELF	0	10
12) LACKING SELF CONTROL	0	10
13) GETTING ON WELL WITH OTHERS	0	10
14) BLEEDING	0	10
15) BREASTS TENDER	0	10
16) FEELING BLOATED/SWOLLEN	0	10
17) PERIOD TYPE PAIN	0	10
18) CRAVING PARTICULAR FOODS (e.g. sweet or salty)	0	10
19) FLG SXL ATR	0	10
20) SXL INTR	0	10
21) SXL ACTV Y☐ N☐ S☐ P☐ I☐	0	10
22) _____	0	10
23) _____	0	10

DRUGS/MEDICATION- Your Oral Contraceptive Pill: YES ☐ NO ☐
Time Taken ☐☐:☐☐

- Other _____

PHYSICAL CHANGES (Other than those mentioned above)

_____

_____

Did anything important happen today to affect the way you feel?

_____

_____

_____

If the way that you felt changed over the day can you describe these changes and their timing? (e.g. Were you energetic in the morning and evening but not in the afternoon? Were your period pains worst at night? Did you feel about the same all day? Etc.).

_____

_____

_____

Figure 3.03 The daily visual analogue scale diary. Not actual size, lines are 100mm long.

measure desire for sexual contact, while "sexual activity" was designed to monitor satisfaction with actual sexual encounters. The three boxes marked S, P, and I were to denote masturbation, sexual activity with a partner, and intercourse, respectively. The reason for making such fine distinctions, apart from a general theoretical interest in the constitution of female sexuality, was to assess whether there might be a relationship between frequency and kind of sexual activity and degree of residual folliculogenesis.

A few other unusual features of this diary were questions relating to day-length, circadian variations in well being, and amount of nicotine and caffeine intake. These were included as exploratory variables, as all were thought to have potential effect on subjective state over time. An analysis of these factors is not included in this thesis.

Instructions about how to complete the daily diary were given verbally at the time of each woman's enrollment interview, and were also given in writing (see Appendix 3.05). It was emphasized that one should not look back at scales from the previous days, as these might influence subsequent ratings. Although it is advised that the order and orientation of VAS which are used repeatedly be varied (Gift, 1989) they were not in this study. The main reasons were practical, because it would have been more costly to produce more than one version of the form. It was also decided that it would be better to risk some response bias than to risk confusing the volunteer and generating invalid data. Volunteers were encouraged, as is advised (Monk, 1989) to practice the diary for one week before the start of the study proper to accustom themselves to the scales. Diaries were collected from volunteers at approximately four week intervals, and were coded using a specially designed template. Values in mm were entered into Microsoft Exel© spreadsheets before being analysed.

3.5.2.2 Methodological considerations of visual analogue scales

Visual analogue scales are considered to be a valid, reliable, and sensitive means of repeatedly measuring moods and physical sensations (Monk, 1989; Gift, 1989; O'Brien, 1987; Casper & Powell, 1986; Luria, 1975; Aitken, 1969; Zealley & Aitken, 1969). VAS are normally presented in the form of a 100mm line, which can be oriented vertically or horizontally (Gift, 1989), upon which the individual is required to make a mark reflecting the degree to which s/he is experiencing a sensation. The two ends of the line represent the extremes of a sensation, but rather than being 'anchored' to some arbitrary linguistic or enumerative point, the poles are intended to represent the extremes within the individual (Monk, 1989). Thus the scale is less vulnerable to

differences in symbolic representations across individuals than nominal or ordinal scales.

The scales may be either bipolar or unipolar. *Apparent* linguistic opposites are normally placed at the ends of a bipolar scale. The difficulty with bipolar scales is that these sensations are not necessarily opposites, or mutually exclusive. Monk (1989) found that while there was a 100% negative correlation between ratings of alert and sleepy in social isolation experiments, there was only a 76% negative correlation between calm and tense, and 68% between happy and sad. While it is immediately obvious on a unipolar scale whether or not the individual is responding sensibly, a mark in the middle of a bipolar scale may be difficult to interpret (Monk, 1989).

Other advantages of VAS are that they are continuous and generate "approximately Gaussian" distributions, for which parametric statistics are appropriate. They are also sensitive to subtle change over time (Monk, 1989; Aitken, 1969). A prime advantage of the technique is that it is very quick and easy for the volunteer (Monk, 1989; Gift, 1989; O'Brien, 1987; Casper & Powell, 1986; Luria, 1975; Aitken, 1969; Zealley & Aitken, 1969). And apart from the more obvious risk of response sets arising from the use of ordinal scales, VAS may be less prone to these by virtue of their ease. Monk (1989) notes that when using a within subject repeated measures design it is very important that the instrument not be "unduly burdensome", as this might itself influence feelings and generate "stereotyped responses". VAS have also previously been used successfully in the assessment of PMS, and have been validated against descriptive scales for this use (O'Brien, 1987; Casper & Powell, 1986, Rubinow, Roy-Byrne, Hoban, Gold & Post, 1984; Sanders, Warner, Backstrom & Bancroft, 1983).

VAS are not without drawbacks. Gift (1989) describes some of these. She notes that "some people find it difficult to convert a subjective sensation to a straight line". And the fact that VAS scales are conceptually difficult for some people is reflected in the fact that a higher percentage of people fail to use them correctly after one explanation than a graphic rating scale. When multiple horizontal scales are used individuals may tend to mark all of them towards the middle, particularly if they are monitoring different dimensions of one sensation. VAS scores may be skewed, however, Gift indicates that significant differences in sensitivity are not detected between scales which are and are not transformed to account for skewness[1]. Although VAS are sensitive, they are

1

relativistic. If an individual marks the maximum for a sensation, but subsequently feels it more intensely, s/he has already exhausted the range of the scale and all future ratings will be inaccurate. The relativism also means that scales are difficult to compare across individuals. VAS are also time consuming for the researcher to rate, as scoring requires that each scale be measured in mm's from the low point of the scale to the mark made on the line.

3.5.3 Enzyme Linked Immunosorbent Assays (ELISA's) for Urinary Steroids

Daily early morning urine (EMU) samples were collected for steroid hormone determination. Antibody-antigen reactions have been exploited to measure the quantity of steroids in bodily fluids such as serum and urine for over thirty years now (Chard, 1987). Conventionally radioactively labelled antigens have been used in competitive binding assays: radioimmunoassay (RIA). Oestradiol and progesterone secreted from the ovary can be reliably measured in human plasma using RIA. More recently assay techniques have become available that allow the the primary urinary metabolites of the ovarian steroids, oestrone-3-glucuronide (E-3-G) and pregnanediol-3-glucuronide (P-3-G), to be measured in EMU samples without the use of radioactivity. Enzyme Linked Immunosorbent Assays (ELISA) use an enzyme labelled hapten and immobilised captive antibody. The bound hapten can be quantified by the optical density reading of the coloured product of the enzyme-substrate reaction.

3.5.3.1 Oestrone-3-Glucuronide ELISA

It has been demonstrated that 95% of serum oestradiol during the menstrual cycle comes from the ovaries, with about 80% from the ovary with the preovulatory follicle, and the rest from the contralateral ovary (Baird, 1970)[2]. E-3-G is one of several urinary metabolites of oestradiol. In studies of ovarian function E-3-G has been shown to be the best metabolite to track because it closely parallels the secretion pattern of oestradiol, and is present in significant quantities in urine (WHO, 1982 [RIA]; Khatkhatay, Sankolli, Meherji, Chowdhury & Joshi, 1988 [ELISA]). Oestrone also correlates well with follicular size, as visualized on ultrasound scan, in ovulatory menstrual cycles (Khatkhatay, et al., 1988).

This may have implications for statistical tests that require data to be normally distributed (eg. ANOVA).

2 The remaining oestrogen comes from the adrenal gland.

At the time when this study was being designed an In-house RIA for E-3-G was used routinely, and an In-house ELISA was being developed by Ian Swanston of the MRC Reproductive Biology Unit, Edinburgh. The performance of the ELISA was compared with the RIA by George Johnston of the NHS Reproductive Endocrinology Laboratories (REL), Edinburgh in March, 1989 and had a high correlation (r=0.99).

The ELISA for E-3-G was performed according to the following protocol. Nunc F-Immuno Plate (GIBCO) microtitre plates were coated with the second antibody, Caprylic acid-purified Donkey Anti-Rabbit Serum (DARS) at a dilution of 1:100 in 0.1M Sodium Carbonate buffer (pH 9.6), and left to incubate for a minimum of 24 hours at 4° C. The DARS was provided by the Scottish Antibody Production Unit (SAPU), and was purified by IS or by the staff of REL. Plates were then blocked with three washes of 0.1% TWEEN 20, after which the blocked plates were washed five times in distiled water and blotted dry.

The primary antibody was Rabbit Anti-Oestrone-3-Glucuronide-B.S.A. Bleed I 9/12/88 which was provided by the MRC/AFRC Comparative Physiology Research Group, Institute of Zoology, London. Label was E-3-G-horseradish peroxidase prepared by IS (lot IS/86). The antibody and label were both stored neat in frozen aliquots at -20° C. Stock solutions of label were made up to a dilution of 1:100 in assay buffer and stored at 4° C for a maximum of four weeks. The working antibody solution was prepared from frozen aliquots of 1:100 in assay buffer. Frozen urine samples were collected from volunteers, thawed and aliquoted into 5ml. Sterilin® vials. These were stored at -20° C until assay.

Reagents and samples were diluted in 0.1M Phosphate Buffered Saline plus Gelatine (pH 7.4). Fifty µl each of label (1:5,000), and antibody (1:45,000) were combined with 100µl of sample (1:100) on the washed plates. This assay was designed for samples to be diluted at 1:200, however, because these women were taking the pill and their basal levels were extremely low all samples were diluted to 1:100 in order that values could be read from a more sensitive portion of the standard curve. Samples were assayed in duplicate, and standards in triplicate. There were 9 standards which ranged from the dose equivalent of 3.9 to 1000 ng/ml.

Once the reagents and sample had been added the plates were sealed and incubated at room temperature for one hour, before the assay incubate was 'flicked out' and washed five times in distiled water as before. A 5mM σ-Phenylenediamine/ 0.03% Hydrogen Peroxide solution was made up freshly for each use in 0.1M Citrate/phosphate substrate buffer (pH5.0). In this temperature and light sensitive step, 200µl of the substrate was added to each well, and the plates were incubated in the dark, at room temperature for 30 minutes. The colour reaction was stopped by adding 50µl of 2N Sulphuric Acid to each well, and the optical density was read using a Titertek Platereader at 492nm. The results were read directly from the Platereader into the Apple Macintosh package Assayzap© and analysed.

The intra-assay coefficient of variation ranged from 5.3 to 6.8%, and the inter-assay C.V. were as follows: low quality control- 25.3%, medium QC-13.5%, high QC-10.8%. It was usually not possible to fit all samples for an individual woman into the same assay. So efforts were made to assay all of a woman's samples on the same day in consecutive assays, using the same batch of standards and reagents. Creatinine is a waste product that is excreted in the urine at a constant rate over 24 hours. E-3-G levels were related as a ratio to creatinine in order to control for the concentration of the urine sample collected. Creatinine (Crt.) levels were assayed in all samples using the alkaline picrate method (Khatkhatay, et al., 1988). Final values were expressed in ng/mg Crt..

3.5.3.2 Pregnanediol-3-Glucuronide ELISA

The rational and procedure for the measurement of pregnanediol-3-glucuronide (P-3-G) is the same as for E-3-G, except that the reagents are specific to P-3-G and the incubation is 2 hours (also see Walker, 1987). Performance was also tested by GJ of REL. No cross reactivity studies were preformed. Comparison with the previous In-house Gas Chromatography, and RIA methods showed a high correlation (0.94 and 0.97 respectively).

The primary antibody for this assay was Rabbit Anti-P-3-G-B.S.A. Bleed F 27/7/87, also from the MRC/AFRC Comparative Physiology Research Group, which was used at a dilution of 1:30,000. The label was P-3-G-Horseradish Peroxidase lot IS/86, used at 1:5,000 in assay buffer. The sample dilution was 1:800, which is the usual dilution for this assay, and was not changed to take account of pill use. The 8 standards ranged from the dose equivalent of 15.6 to 2000 pg/100µl. All other procedures are as above.

The intra-assay coefficient of variation ranged from 3.8 to 4.6%, and the inter-assay C.V. was as follows: low quality control- 26.1%, medium QC-8.9%, high QC-12.6%. Final values were expressed in pg/mg Crt..

3.5.4 Analysis of the Visual Analogue Scores and Hormonal Data

The difficulties of analysing data derived from daily self-ratings of well being were considered in Chapter Two. Because there is no uniformly accepted statistical procedure to deal with such data, the techniques used to analyse the data reported in this chapter are based on the research questions outlined in section 3.2. Thus the analysis is directed at 1) detecting cyclical change over time in volunteer's well being, 2) comparing the degree of variation between the two pill groups, and 3) relating well being to endogenous steroids. A variety of different, complimentary methods were used. Statistical advice was sought from two local statisticians: Jim Slattery (JS, Clinical Trials Unit, Western General Hospital, Edinburgh) and Pamela Warner (PW, Behaviour Research Group, MRC Reproductive Biology Unit, Edinburgh). Some of the analyses were carried out by Jim Slattery, which are indicated below.

3.5.4.1 Principle components analysis of visual analogue scores

A large number of variables were measured by the VAS diary. So in an effort to examine the manner in which the scales related to each other and to reduce the large number of data points generated over the study, a factor analysis was carried out. Principle components analysis (PCA) is a mathematical method which essentially performs concurrent correlation and regression analyses on a body of data to determine the relationship of the variance of the factors to one another. It has two potential uses: data reduction and data description. With regard to data reduction, if the first few components account for a large part of the variance then "the observed variates may be replaced by a smaller set of derived variates....without serious loss of information" (Maxwell, 1977). In a "successful" PCA a large proportion of the variance in the data is explained by the top six, or fewer, components. The proportion of variance explained may be as much as ninety per cent (90%) or more. In addition, the first unrotated component may explain the majority of the sample variance and contain weightings for all the variables in the analysis. The first component thus may represent an overall summary variable of the data set.

The main purpose of the PCA in this investigation was to reduce the dataset, and a secondary aim was to compare the two pill groups. The analysis was carried out by JS using the Bio-Medical Data Processing package (BMDP) in the manner outlined in section 18.1 of the BMDP manual (pp. 480-485, Dixson, Brown, Engelman, Frane, Hill, Jennrich & Toporek, 1981). Separate analyses were carried out to compare the diary results of the two different pill types and then a second analysis was undertaken including all women. Both unrotated and orthogonally rotated components were derived. As will be discussed in the results section below, the PCA did not succeed in explaining the majority of the variance, therefore only the top two component scores relating to affect were used to condense the data for subsequent analyses.

3.5.4.2 Standardization of pill cycle length and division into phases

In addition to reducing the number of diary scales into several components, it was also necessary to standardize the length of women's cycles so that cycles of different lengths might be sensibly compared. Further, because it is conceptually easier to deal with a number of defined phases of the cycle across individuals than to describe daily data points, the diary and hormone data were broken up into a number of meaned phases.

Cycle length was standardized according to the procedure described by McCance, Luff, and Widowson (1937). This involves adjusting cycle length by weighting each day so that all cycles become 28 days long by dividing the actual cycle day by the total cycle length and then multiplying by 28 to create a fraction which is rounded to the nearest whole number. This way if a cycle is shorter than 28 days the appropriate number of days are omitted from the string, while if it is longer the appropriate number of days are duplicated. While this is a purely mathematical procedure, it has the advantages that it is not arbitrary, and when used in conjunction with the generation of phase means, no data points are lost.

In this study a "cycle" was taken to be the interval from the onset of one withdrawal bleed to the next. Unlike the menstrual cycle, the pill cycle is highly circumscribed in length because it is 'driven' by the regime of 21 days exogenous steroids plus seven days off. Therefore a technique which standardizes cycles to 28 days is meaningful in this case. If one discounts breakthrough bleeding, withdrawal bleeding as a consequence of the pill free interval, almost always occurs within a specified number of days from the cessation of active tablet taking. Although there may be some variability

in cycle length from one bleed to the next within the individual it is not likely to be more than a few days.

There is considerable debate and inconsistency about the appropriate way to divide the menstrual cycle into phases. Generally, phases are determined arbitrarily with regard to the timing of menstrual bleeding based on the clinical impression of the timing of cyclical symptoms, in order to "capture" symptoms in one phase, and exclude them from others. Once again the transformation used here was purely mathematical. Cycles of diary ratings and hormone values were divided into seven mean phases of four days each, beginning at day one of withdrawal bleeding. In cycles greater or less than 28 days the phases were weighted according to the standardization procedure described above. In short cycles some phase means are made up of only three data points, while in long cycles some are made up of five data points.

While these phases may not be as physiologically meaningful as those of the menstrual cycle, certain endocrine events clustered in particular phases: Phase 1) bleeding; Phases 2 or 3) rising endogenous oestrogen; Phases 3 or 4) suppression of endogenous oestrogen to baseline by the exogenous steroids; Phases 4 to 6) basal endogenous steroid levels; Phase 7) pill withdrawal and the endocrine events which precipitate withdrawal bleeding.

3.5.4.3 Calculation of the standard score *z* for the PC's

Because VAS are relative to the individual who is using them it is likely that the raw scores across all volunteers will not be normally distributed. In order to use parametric statistical tests raw scores for the principle components were converted into *z* scores. The standard score *z* expresses data points as a number of standard deviations from the group mean. (z = {raw score - group mean for variable}/ SD of the group mean for variable). The final unit is the number of standard deviations, and may therefore be positive or negative. Certain assumptions are made with the use of *z* scores: 1) the population from which the distribution of scores arises is assumed to have equal means and dispersions in all variables measured, and 2) the form of the distribution in terms of skewness and kurtosis (height) must be very similar from one variable to another (Guilford, 1965). In practice, it is virtually impossible to determine if these assumptions are met by the data, therefore, one must proceed as if they were. Even within these limitations it is likely that the standard scores provide more "nearly comparable" values than raw scores , although the procedure does not normalize the

distribution (Guilford, 1965). The *z* scores for the top two principle components (PCs) were used in all the subsequent analyses.

3.5.4.4 Analysis of transformed diary data and hormone parameters

A number of different analyses were undertaken using the principle components, and transformed diary ratings and hormone results. Descriptive statistics (eg. mean, standard deviation) were used along with analysis of variance (ANOVA) techniques, and tests of significance, such as t-tests. The discussion that follows focuses on uni- and multivariate analysis of variance. Other methods used in the chapter are described in the relevant results sections.

ANOVA is a statistically powerful means of investigating significant differences across groups, time, or experimental situations. Parametric tests assume the independence of observations, equal dispersion of variance across groups, and normal distribution of data within groups. Daily diary ratings may not be independent from one day to the next and hormone levels certainly are not. Equally there is likely to be a trend in consecutive ratings that may produce type one error. This problem can be overcome by combining time points. This technique is used in this thesis by the creation of mean phases.

ANOVA was used in three different ways with this data set. In the first case univariate tests were carried out on the standardized phased data for all women for all diary scales and principal components 1 and 2 in order to assess the relationship of subjective state to bleeding and to endogenous oestrogen within the individual. In one set of tests, the phases entered into the analysis began with the first bleeding episode in the first pfi of the study. This analysis was directed at assessing a phase effect over the cycle relative to bleeding, within the individual. The repeated measure in this analysis was the two cycles, with seven phases each. In the second set of tests the mean phases were aligned by the phase in which endogenous oestrone reached its peak. This may be seen as analogous to centring menstrual cycle data around the time of ovulation. The object of this analysis was to determine whether or not subjective state variables varied predictably relative to E-3-G levels. In those women for whom oestrogen peaked in the same phase in both cycles, the data remained temporally continuous. However, for some women one phase had to be repeated or omitted in order to position the peak at the same time point in both cycles. This arguably distorts the data, however, it is a means of determining whether or not there is regular change in well being in relation to

steroids as opposed to bleeding. These analyses were carried out on the University of Edinburgh main frame computer using the Statistical Package for the Social Sciences, second edition (SPSS-x).

The second ANOVA was ANOVA for repeated measures which was carried out for each principle component at the group level (monophasic versus triphasic) by JS using BMDP on the main frame to examine whether or not there was significant fluctuation in any component over the cycle. E-3-G was entered as a covariate, and pill day as a twenty-eight (28) level categorical variable in order to test the relationship of change in subjective state over time to E-3-G. He compared bleeding and non-bleeding days, pill types, self-reported PMS status, and gynaecological age within the sample.

Finally, multivariate ANOVA (MANOVA) was undertaken using SPSS-x for selected variables and principle components. MANOVA has the advantage over multiple univariate tests that it takes into account possible correlations and differences in variance between all the variates at once (Maxwell, 1977). Four different groupings of volunteers were generated on the basis of distinct aspects of oestrogen dynamics. These were organized around potentially biologically meaningful aspects of oestrogen change, and are described in the results section below. The analysis had a 2 or 3 (group), by 2 (cycle) by 7 (phase) design. The between subject effect was the 'group', and 'phase' and 'cycle' were the two within subject effects. The phases were oestrogen-peak-centred in the manner described above. SPSS was used to carry out tests to detect the homogeneity and sphericity of the data. These are the "symmetry conditions" which must be met if MANOVA is to be used and are the same as those for ANOVA (Hand & Taylor, 1987; Guilford, 1965). The SPSS analysis allows a number of *post hoc* univariate test statistics to be calculated following the multivariate tests, which have more degrees of freedom, and therefore greater statistical power. The *post hoc* tests used in this analysis are described in the results section below.

3.5.5 Final Semi-Structured Interview

A semi-structured interview was conducted with each woman in her home after the ten weeks of monitoring had ended. The purpose of this interview was to allow women to describe the attitudes and beliefs which they hold about vaginal bleeding, contraceptive use and other reproductive and gender issues. It is widely acknowledged that psycho-social factors may influence women's responses to and reporting of their reproductive

experience. However, the nature of attitudes and beliefs, the range of ideas women hold, and the mechanisms by which these modulate experience and reporting have not been adequately researched in the past. Although not the primary research aim of this thesis, the information gathered from these interviews provided insight into the social and personal psychological context in which the more experimental studies were carried out. At a practical level interview material was used to generate the second version of the MHRAQ, that in addition to providing valuable information in its own right, links this investigation with a subsequent study. Interviews took about one hour, were audiotaped, and later transcribed. The development of the interview schedule, details of the qualitative interview technique, and the results are discussed in detail in Chapter Four.

3.6 Results

3.6.1 Sample Size and Coding

Twenty women enroled in the study and four women dropped out during the ten weeks of monitoring. These four were replaced using the same recruitment procedure in order to maintain groups of ten women on each formulation. All four dropped out because they did not wish to, or were not able to meet all the study demands. Notably they found daily urine collection and storage onerous. Volunteers were given consecutive code numbers as they entered the study to denote which type of formulation they were using. Thus, volunteers are referred to throughout the text by their code numbers: M1 to M10 for the ten monophasic takers, and T1 to T11, excluding T5 for the triphasic takers.

3.6.2 Volunteer Characteristics: Results of MHRAQ-1

The biographical details which are directly relevant to this study including pill taking history and reported experience of cycle-related change are reported here. Other characteristics of volunteers, aspects of experience, and attitudes are reported in Chapter Four. General demographic information is contained in Table 3.01, which also compares the monophasic and triphasic groups. The majority of volunteers were in their mid- to late twenties, married or living with a partner, well educated, in full-time white collar employment, nulliparous, and protestant but not active in their religion. There were no significant differences between the two pill groups except in

the duration of pill use. The monophasic takers had used OCs for significantly longer than the triphasic takers which probably reflects the fact that the monophasic takers were slightly younger when they started using the pill and they were slightly older on average. All twenty women who completed the study were taking the pill for contraception, although two initially started it due to irregular and/or painful periods, and one also used it to control her PMS.

The mean age at menarche for the monophasic takers was 12.5 years (SD1.3) and 13.1 years (SD1.7) for the triphasic takers. The overall range of ages at which first periods occurred was between 10 and 16 years (10-15 mono., 11-16 tri.) with a mean of 12.8 years (SD1.5). Gynaecological age is the number of years between menarche and the present, or number of years of menstrual cycles. After seven years of cycling "gynaecological maturity" is assumed to have been reached (Metcalf & MacKenzie, 1980). Thus, with gynaecological maturity the likelihood that ovulation will take place in any given cycle, and that the cycle will be of an appropriate length to be potentially fertile is 90% or greater. Because the monophasic takers were slightly older, and had slightly earlier menarche, they were gynaecologically older. While most volunteers were gynaecologically mature when they entered the study, they were not generally mature when they started taking the pill. This fact has potential implications for the amount of residual ovarian function that one might observe during a pill cycle, which in turn has relevance for the study of its relationship to subjective state[3].

3

It is not known whether gynaecological maturity is a straightforward function of chronological age, or a process which is affected by interruptions to ovarian cyclicity such as pill taking, or pregnancy and childbirth. (Baird, 1989 *personal communication)* It is not clear, for example, that a woman who has had five years of natural cycles and five years of pill use since menarche is the same as a woman who has had ten years of uninterrupted natural cycles. The fact that women who have and have not taken the pill do not differ significantly in the time at which they reach the menopause (Batzer, 1984) however, suggests that ovarian maturation is dependent on time rather than duration of natural cycles. If this is the case then most of the women in this study, based on their ages and the number of years since their menarche, might be expected to experience a normal ovulatory cycle if they were not currently using the pill.

Table 3.01 Biographical Details of the Sample: Comparison of the two pill types

Variable	Classification	Monophasic	Triphasic	Signif.
Age	mean years (range)	27.3 (19-34)	26.6 (21-35)	NS
Relationship status	Married/Cohabiting	n=7	8	NS
	Single	3	2	
Education	School leaver/Highers	3	2	NS
	University/Poly etc	7	7	
	Postgraduate	0	1	
Occupation	Scientist/Engineer	1	2	NS
	Nurse/Social Work etc	3	3	
	Management/Admin.	2	3	
	Secretary/Support etc	3	1	
	Student	1	0	
	Actress	0	1	
Religion	Protestant	5	7	NS
	Catholic	2	1	
	None	3	2	
Parity	Nulliparous	10	10	NS
Time on pill	mean years (range)	9.8 (3-17)	5.7 (3.5-9)	p=0.018
Gynae. age	mean years (range)	14.8 (4-21)	13.5 (6-22)	NS
Gyn.age on pill	mean years (range)	5.2 (1-10)	6.6 (3-15)	NS
Bleed volume	Light	4	4	NS
	Moderate	6	5	
	Heavy	0	1	
Bleed duration	mean days (range)	4.2 (2-6)	4.5 (3-6)	NS
Pill effect on bleeds	Lighter	7	8	NS
	No effect	0	1	
	Heavier	1	0	
	Don't know	2	1	

Note- Significance levels indicate whether or not there is a significant difference between the two groups for each variable, and relate to t-tests or Chi square tests as appropriate. Gynae. age= Age - Age at menarche; Gyn.age on pill= gynaecological age at first pill use.

The most frequent average duration of vaginal bleeding reported by the sample was four or five days (80% of women), and most women reported moderate or light blood loss.The majority also reported that OC use had made their bleeds lighter and less painful. The two pill groups were not different with regard to the length or volume of bleeding. One woman in this sample (M3) routinely takes three to four packets of pills in a row (the "tricycle regime"), and so has been excluded from subsequent analyses relating to the timing of bleeding.

3.6.3 Self Reported PMS Status in Relation to Neuroticism

On the MHRAQ-1 volunteers were asked whether or not they considered themselves to have PMS (see Appendix 3.04). The possible replies were 'yes', 'no', 'maybe', and 'don't know'. The distribution of replies is shown in Table 3.02 below.

Table 3.02 Self Designated Retrospective PMS Status

Pill Group	Yes	Maybe	No	Don't know
Monophasics	1	3	5	1
Triphasics	5	4	1	0
Total	6	7	6	1

There was no significant difference between the two pill groups for Neuroticism (N) or Extroversion (E)[4]. The mean monophasic N score was 10.8 (SD5.6) and the mean triphasic N score 10.5 (SD5.6), t=0.12, p=0.91. Similarly, the mean monophasic E score was 14.4 (SD2.2) and the mean triphasic E score 13.0 (SD5.0), t=0.81, p=0.43. Thus the overall means for the sample were N 10.7 (SD5.5) and E 13.7 (SD3.8) which are both slightly higher than the normal population means given by Eysenck & Eysenck (1964) at N 9.1 (SD4.8) and E 12.1 (SD4.4). Eysenck & Eysenck (1964) indicate that women tend to score slightly higher on N than men, and lower on E, but they do not quantify the amount of difference. The N scores in this sample are consistent with the

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One quarter of women had lie scale scores of 4 or 5 (1mono., 4 tri.), which is the suggested cut-off point for accepting the inventory responses (Eysenck & Eysenck, 1964). No L scores exceeded 5, and therefore no woman's scores were excluded from the analysis.

expected sex difference, and the higher E score in this group probably reflects the fact that extroversion is likely to be a prerequisite for participation in a study of this kind.

Because neuroticism has previously been related to cyclical symptoms, N scores on the EPI were compared with retrospectively reported PMS status. A Student's t-test showed that women who said 'yes' or 'maybe' to PMS had significantly higher N scores than women who said 'no' or 'don't know': Yes/Maybe mean N 12.8 (SD4.9), No/Don't know mean N 6.7 (SD4.2), t=-2.75, p=0.01.

3.6.4 Description of Hormone Results

Most volunteers complied very well with daily urine collection. Six individuals produced all 70 samples. The largest number of missed samples was 17 or 24%. The mean number of samples missed by the monophasic group was 3.5, and 4.9 by the triphasic takers. As a rule missed samples were dispersed over the whole study and therefore no woman was excluded due to inadequate sample numbers. Hormone values in this section are dealt with as daily measures, and the 'analysis' is largely descriptive. Two women extended the length of their pill cycle. M3 (see above) and T3 who took a course of antibiotics during the 6th week of the study, and was advised by her doctor not to have a pill free interval. The effect of these changes on steroid levels are discussed here, but these individuals have been excluded from the subsequent analysis of daily diary scores in relation to hormones.

Figure 3.04 shows the mean E-3-G and P-3-G levels for the monophasic and triphasic takers over two complete cycles. A Students t-test shows that there is no significant difference between the groups for oestrone: t=0.97, p=0.33. As expected, the bulk of endogenous oestrogen was secreted during the pfis and the first weeks of pill taking. All women showed some degree of response, although its magnitude and timing varied considerably across women. If ovulation has occurred P-3-G levels will show a sustained rise over 1.5-2.0 pg/mg Crt.. In these women levels were extremely low at all phase of the cycle. Within the individuals P-3-G oscillated slightly around a unique baseline level, but there were no sustained rises observed, and it was concluded that no one had ovulated. So, although the two pill groups differed significantly in P-3-G level (t=14.82, p=0.00) it is unlikely that the difference is clinically significant. The overall daily mean levels of steroid are presented in Figure 3.05.

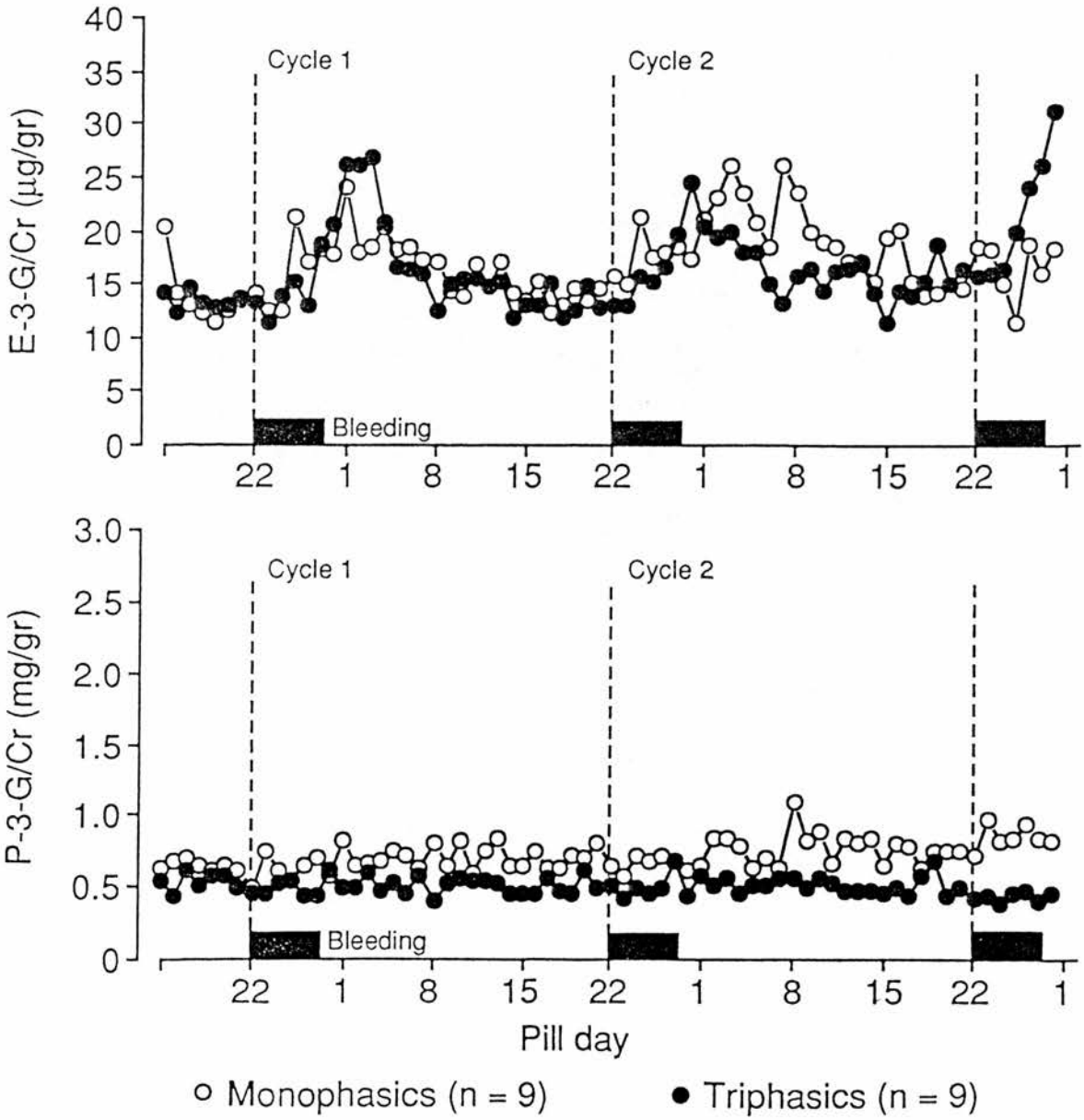

Figure 3.04 Comparison of daily oestrone and pregnanediol levels by pill type over two consecutive pill cycles.

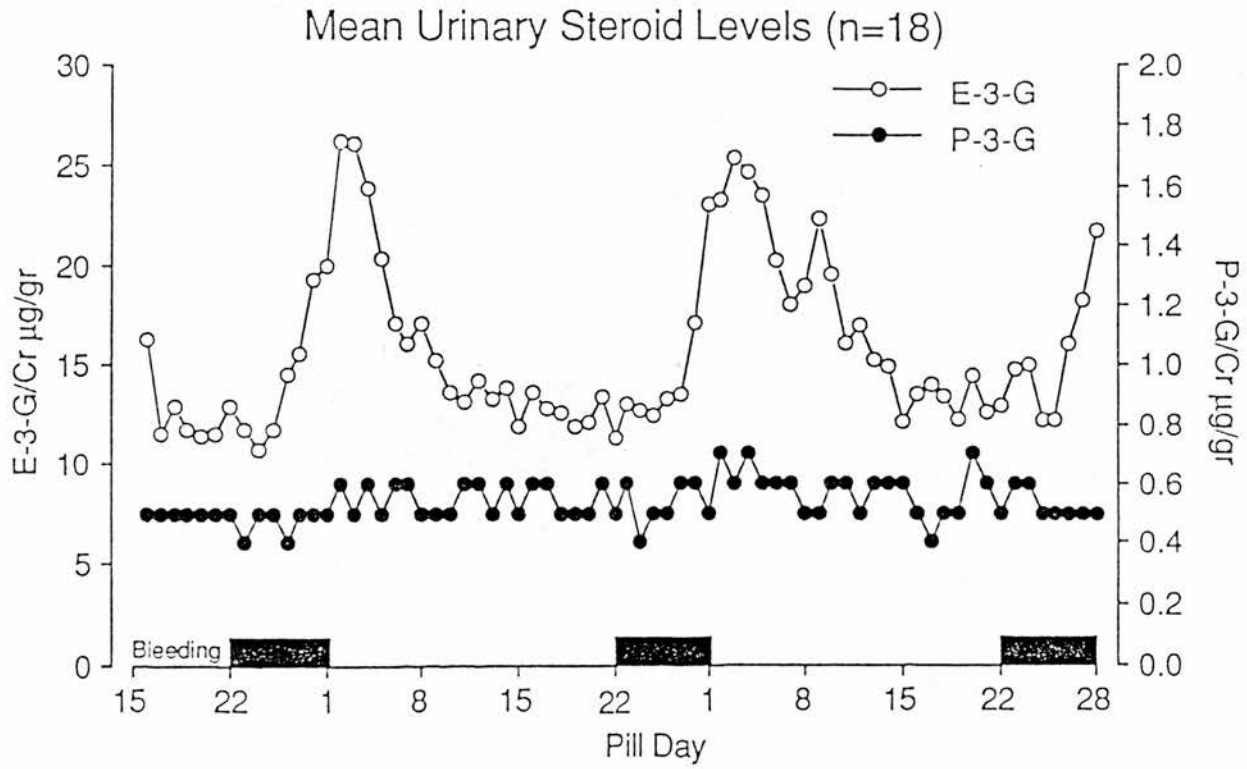

Figure 3.05 Mean daily urinary steroid levels for all folliculogenesis study volunteers over two consecutive pill cycles.

Eight of the 18 women who had two normal pill cycles showed a clear pattern of cyclical oestrogen rising in the pill free interval of both cycles. Figure 3.06 shows the individual profiles for two women on each pill type. The plot for T9 illustrates that the magnitude of peak oestrogen may vary from one cycle to the next, however, most women show uniformity over time. Figure 3.07 gives examples of the other ten profiles in which E-3-G oscillated erratically over the cycle, and in which the pfi seemed to have a limited effect on release from suppression. The very low overall levels for these women contrast with high baseline and peak levels achieved by the women shown in Figure 3.08. Volunteer M1 experienced a sustained rise in oestrogen which peaked in the second week of pill taking, and did not return to baseline until the beginning of pill week three. The only other woman who showed considerable oestrogen change was T3, mentioned above. She had raised E-3-G well into the third week of pill taking after the first pill free interval. Curiously, this rise occurred before she took a course of Erythromycin® which might have interfered with pill absorption. Neither of these women had progesterone changes indicative of ovulation.

The peak was defined as the highest single value occurring between day one of the pfi and day eight of pill taking. Figure 3.09 shows the distribution of the timing of peaks. The distribution is skewed towards the pfi but the commonest day for E-3-G to reach its maximum is day 2 of pill taking. There were no significant differences in the peak E-3G values achieved by the two pill groups: monophasic mean peak 34.1µg/gr (SD18.9) and triphasic mean 34.4µg/gr (SD17.8), t=0.06, p=0.95.

3.6.5 Analyses of Prospective Daily Diary Ratings and their Relationship to E-3-G Profiles

3.6.5.1 Amount of usable data and the distribution of cycle lengths

In this sample the interval between stopping pills to beginning to bleed was 2.35 days for the monophasic takers, and 2.08 days for the triphasic takers. Consequently, 56% of cycles were 28 days long, and the other 44% of cycles were 28±1-2 days. In the few cases where breakthrough bleeding occurred towards the end of the pill packet (mono. n=1, tri. n=4), and ran on into the pill free interval, the first day of the pill free interval was taken as cycle day one. In addition to the 2 women with extended cycles two cycles were incomplete because diary keeping did not continue until the onset of the final bleed (M2 and T4). The data for these two women were used where there were sufficient phases for the analyses, eg- the first cycle was used in group analysis.

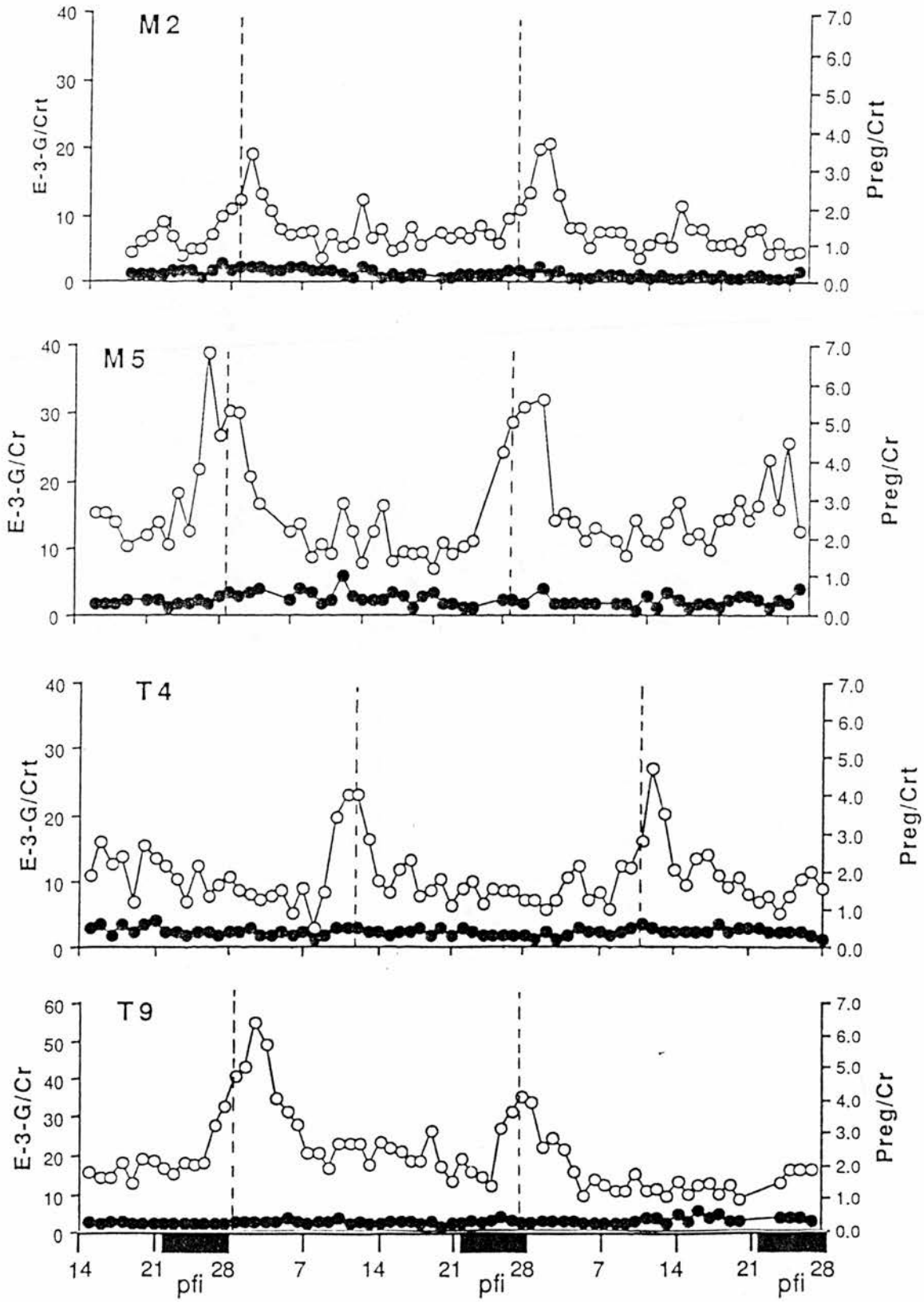

Figure 3.06 Individual urinary steroid profiles for two women in each pill group who show clear patterns of oestrone secretion in response to the withdrawal of pill steroids during the pill free interval. Dotted lines indicate the day active pills were resumed.

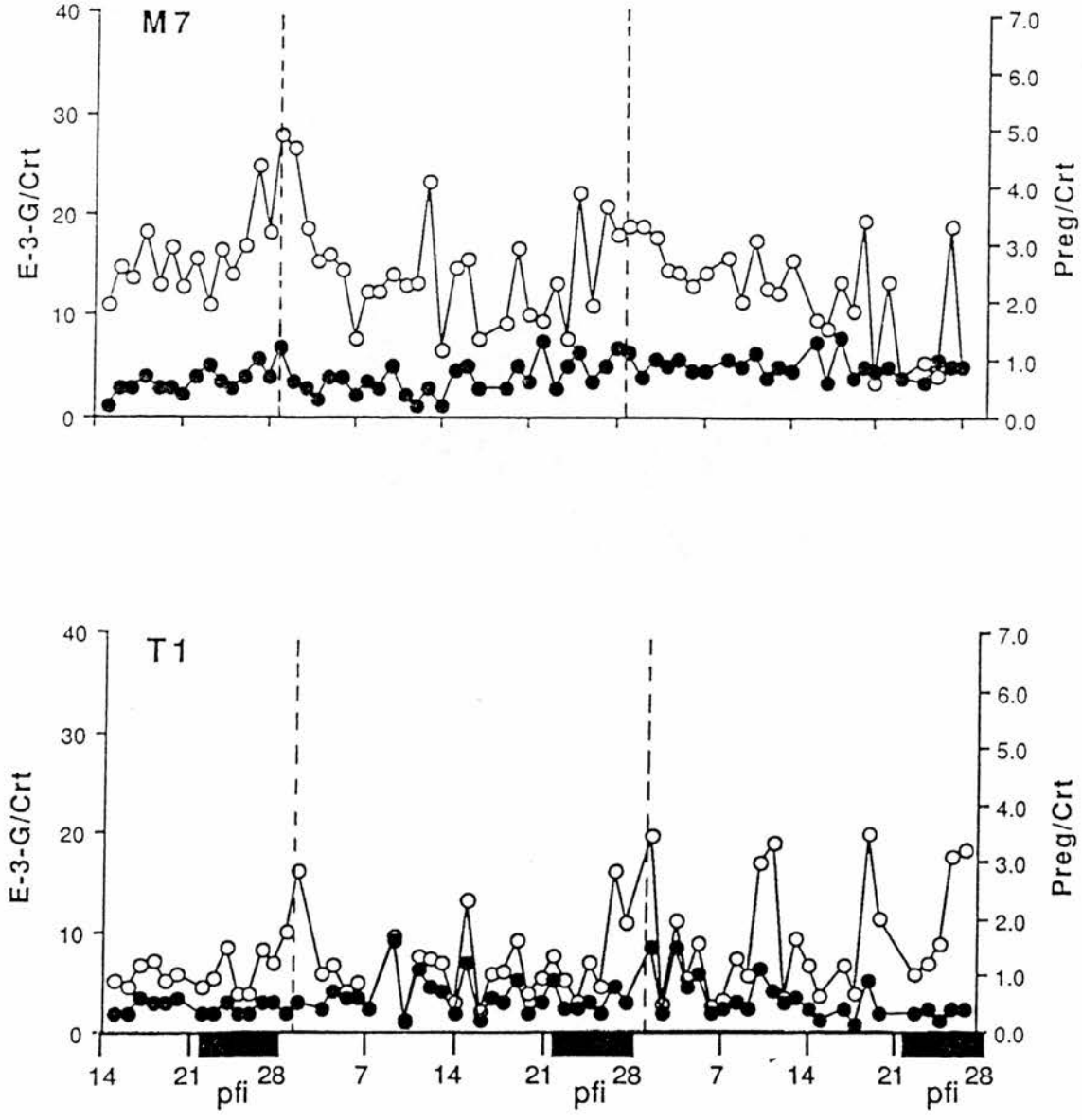

Figure 3.07 Individual urinary steroid profiles for one woman in each pill group who showed erratic patterns of oestrone secretion, with no apparent relationship to the withdrawal of pill steroids during the pill free interval. Dotted lines indicate the day active pills were resumed.

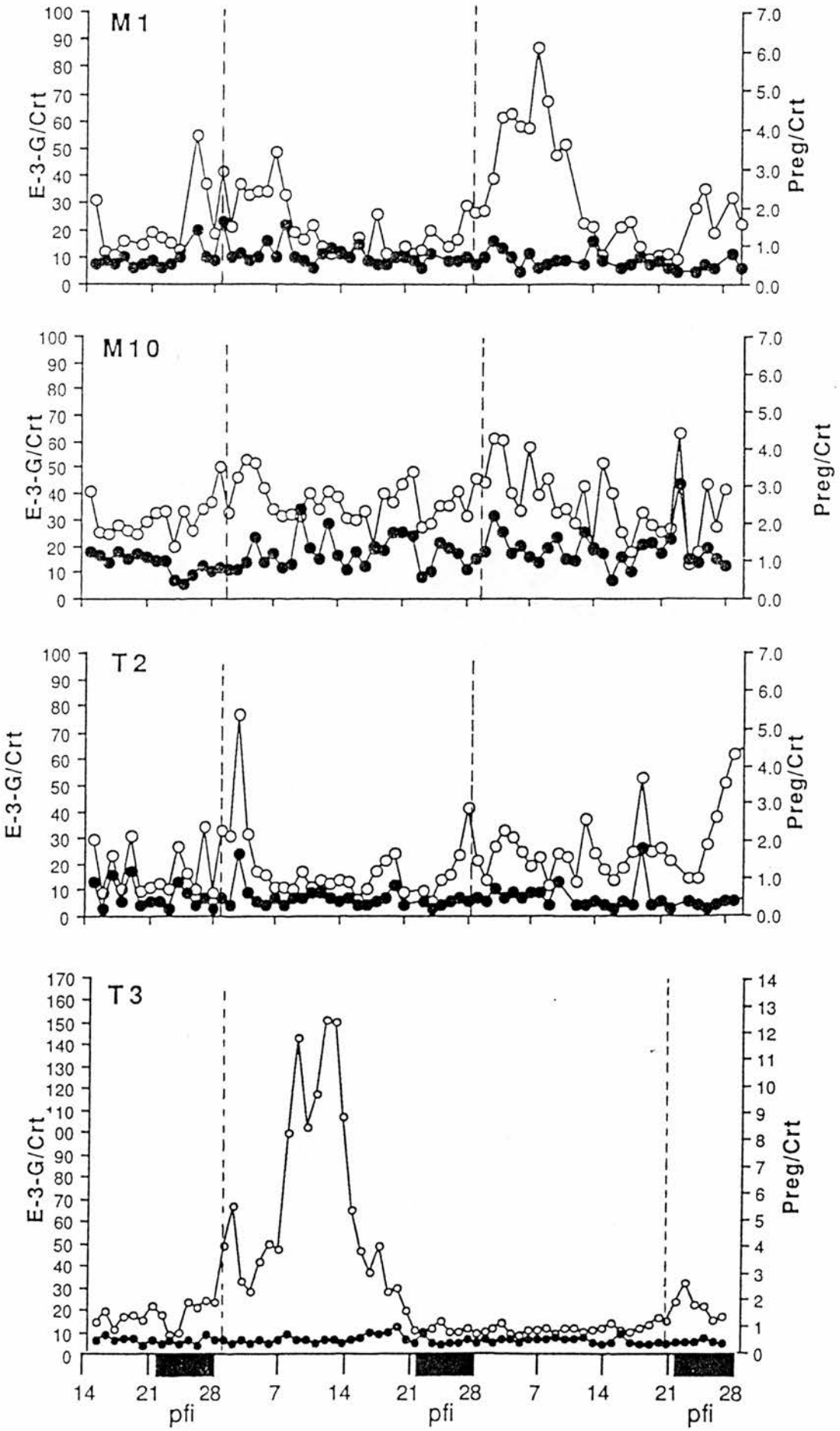

Figure 3.08 Individual urinary steroid profiles for those women who showed high baseline and peak levels of oestrone secretion. Dotted lines indicate the day active pills were resumed.

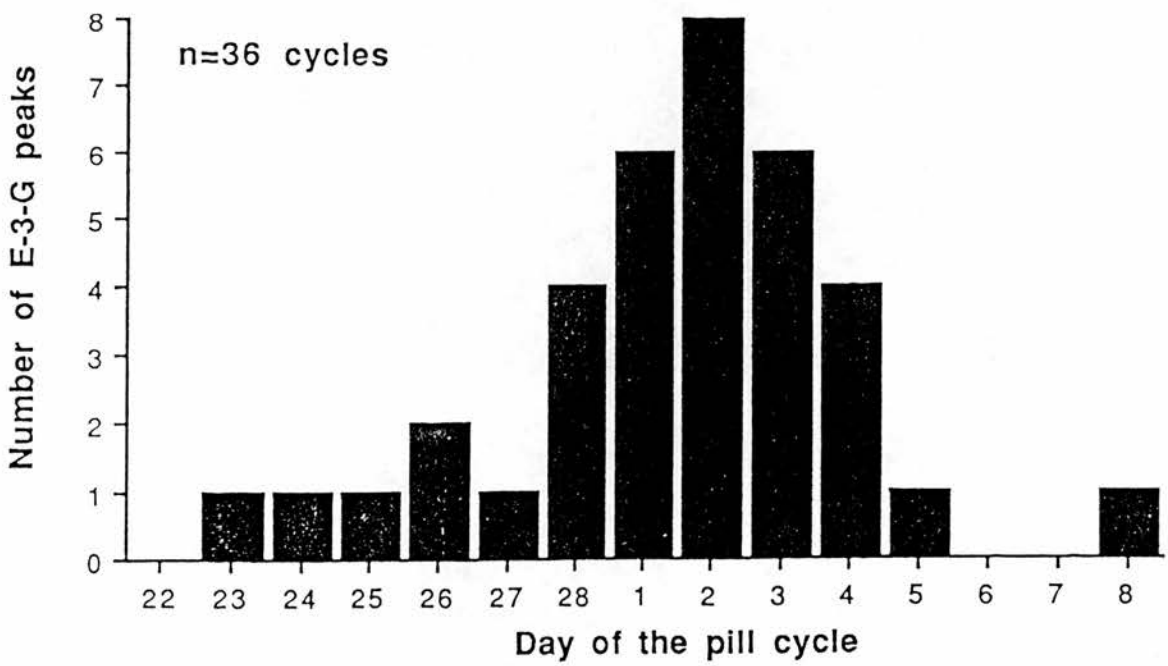

Figure 3.09 The distribution of peak oestrogen values by day of the pill cycle for 36 cycles.

3.6.5.2 Principle components analysis for data reduction

Separate principle components analyses were carried out for the two different pill types (n=9 in each) by JS, but there was no difference between them in terms of the amount of variance explained by the factors, or the grouping of variables. Thus a second analysis was undertaken including all women (n=18). The results that follow are derived from this whole sample analysis.

Both unrotated, and orthogonally rotated components were derived. The rotated and unrotated components did not differ very much in the proportion of the variance which they explained or the weighting of individual variables. This implied that the 'rotation' had not changed the components substantially. So, for this reason and the apparently conceptually meaningful nature of the rotated components, these were used in subsequent analyses. This analysis was moderately successful as a data reduction exercise, explaining about 67% of the variance in the data in the top six components. The results of the analysis were as follows:

Top 6 factors for 18 cases, explaining 67% of the variance.

Factor	**Eigen value**	**Per cent variance explained**
1) Feeling good about yourself	0.857	
1) Cheerful & happy	0.836	
1) Getting on well with others	0.836	
1) Energetic & active	0.801	
1) Creative	0.764	
1) Relaxed	0.686	**23.7%**
2) Irritable	0.820	
2) Mood up & down	0.793	
2) Aggressive	0.769	
2) Tense & anxious	0.722	
2) Depressed & unhappy	0.706	
2) Lacking self control	0.651	**16.4%**

Factor (continued)	**Eigen value**	**Per cent variance explained**
3) Sexual interest	0.877	
3) Sexual activity	0.787	
3) Feeling sexually attractive	0.716	**8.2%**
4) Feeling bloated/swollen	0.868	
4) Period type pain	0.830	**7.7%**
5) Craving particular foods	0.809	
5) Breasts tender	0.634	**5.8%**
6) Day length	0.775	
6) Not fatigued & tired	0.581	**5.0%**
		Total= 66.9%

Eigen values listed here if they exceeded 0.5.

These factors are conceptually meaningful. The first and second factor seem to represent a positive affect component (PC1) and a negative affect component (PC2), respectively. Factor three clearly shows that the three indices of sexuality covary. Factors four to six indicate relationships between various parameters of physical well being. All twenty-one scales are accounted by these six factors. PCs 1 and 2 will subsequently be referred to as positive and negative affect.

3.6.5.3 Detection of cyclical change in individuals

A) Change from the premenstrual to the postmenstrual phase. Pre- to postmenstrual change scores were calculated using the '30% rule' (Hamilton, et al., 1984) as a means of assessing how many women in this sample experienced notable changes in particular mood or physical parameters around the time of bleeding. The mean of the two phases preceding the bleed were compared with the mean of the two phases following the bleed in both cycles for negative and positive affect[5], and for the four physical symptoms: breast tenderness, bloating, period pain, and food craving. These were considered separately because they explained such a small proportion

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Standard *z*-scores used.

(<10% each) of the sample variance within principle components 4 and 5, and because they may have different aetiologies.

The data which are summarised in Table 3.03 below represent the percentage change in physical variables based on the range of the scale used by that individual. Thus change values are only indicated 1) if there was at least a thirty per cent change from the pre to postmenstrual phase for that variable, and 2) if the individual used at least one third of the possible range of the visual analogue scale in question.

Table 3.03 Pre to Post Menstrual Change in Physical State (n=18)

	% Reduction for those women who showed ≥30% change													
	M2		M6		M10		T7		T8		T10		T11	
symptom	Cy1	Cy2	Cy1	Cy2	Cy1	Cy2	Cy1	Cy2	Cy1	Cy2	Cy1	Cy2	Cy1	Cy2
Brsts tender	nc	58	**86**	**35**	nc	39	**74**	**45**	nc	38	nc	nc	nc	nc
Bloating	nc	nc	nc	nc	nc	nc	**63**	**34**	**43**	**30**	**100**	**30**	nc	nc
Period pain	nc	nc	nc	37	nc	nc	34	nc	nc	nc	nc	nc	nc	nc
Cravings	nc	nc	100	nc	37	nc	nc	nc	nc	nc	nc	nc	nc	36

Key: Cy1- cycle 1, Cy2- cycle 2, Brsts tender- Breasts tender, nc- no change of ≥30%, figures in bold indicate those women who showed ≥30% change in both cycles

Of the seven women indicated above only four showed notable pre to post change in both cycles for a given symptom, either breast tenderness or bloating. All symptom scores were worse premenstrually and improved or returned to zero after bleeding. Cyclical change in breast tenderness and bloating were more common than period pain or food craving (7/14 cycles and 6/14 cycles versus 2/14 cycles and 3/14 cycles).

Eight additional women's scores changed by at least thirty per cent from the pre to postmenstruum. However, their actual scores never exceeded 33mm on the visual analogue scale, so their level of symptom experience was very low, and these data are not included in the table. Amongst these women breast tenderness and bloating changed by ≥30% of their range in eight cycles each, and period pain and cravings in two and seven cycles respectively.

The Table 3.04 summarizes the pre to post menstrual change scores for positive and negative affect. The principle component scores for pre and postmenstrual phases were

calculated for each woman on the main frame computer using a fortran programme written by Dilys Rennie (DR). Scores were generated for the cycle phases using the daily data weighted according to the eigen values from the whole-group factor analysis. Only eigen values of ≥ 0.250 were included. Individual factor scores were then transformed to *z* scores. Only those women with at least a thirty per cent change in at least one of the components are included in the table. The sign of the number indicates whether the component improved (+), or worsened (-) from the pre to postmenstruum. In classical PMS, one would expect positive affect to have increased and negative affect to have decreased.

Table 3.04 Pre to Post Menstrual Change in Mood State (n=18)

	% Reduction for those women with ≥30% change in mood							
	M4	**M5**	**M7**	**M8**	**M9**	**M10**	**T1**	**T2**
Factor	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2	Cy1 Cy2
Pos.affect	+36 nc	nc +39	+70 nc	nc -51	nc -47	**-41 -42**	-32 nc	-41 nc
Neg.affect	**+40 -71**	nc -62	**-46 -54**	-31 nc	nc nc	**+34 -35**	nc nc	+60 nc
	T4	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	
Pos.affect	nc -35	nc -46	nc +64	nc nc	nc +60	nc nc	**+77 +32**	
Neg.affect	nc nc	nc -31	nc nc	nc -31	-65 nc	nc -40	nc -33	

Key: Cy1- cycle 1, Cy2- cycle 2, Pos.affect- Positive affect component, Neg.affect- Negative affect component, nc- no change of ≥30%, signs indicate the direction of change from pre to post menses, figures in bold indicate those women who showed ≥30% change in both cycles

Very few women showed at least a thirty per cent change in both cycles. Only two women were cyclical by this criterion for positive affect: M10 and T11. T11 was happier after bleeding in both cycles, yet M10 was actually less happy. Only M7 had substantially lower negative affect scores after bleeding in both cycles. Negative affect changed by ≥30% for M4 and M10 in both cycles, but in opposite directions on the two occasions. Overall, positive affect did not change in the expected direction. In eight out of fifteen cycles with ≥30% change, mood was less positive after bleeding than before. On the other hand, in 11 out of 14 cases where negative affect changed, mood was less negative after bleeding.

The women in this study were not selected for perimenstrual change, however, twelve of the eighteen women whose data could be included in the analysis indicated that they

definitely, or maybe had PMS. All of the 12 women who said 'yes' or 'maybe' they experienced cycle related change, confirmed that experience to some degree according to the 30% change rule showing at least some variability in affect. In the group of women who said 'no' they did not have PMS, five out of six also showed a 30% change in some variable. However, unlike the PMS reporters not all of them 'confirmed' on the mood variables. Three of these women did show evidence of cyclical mood, but two only changed in physical state, and one had no changes.

B) Univariate analysis of variance (ANOVA). Two sets of univariate ANOVA were carried out on the standardized phased data for all women for all diary scales and *z* scores for PC's 1 and 2. In the first analysis the phases were compared over the two cycles in an effort to uncover whether or not individual women showed consistent symptom timing.

The variables for which individuals showed cyclicity varied considerably, and no trend emerged for particular symptoms, or by pill type (see Table 3.05) There was also little concordance with the woman's retrospectively reported worst 'symptom/s'. Menstruation most often occurred in the same phase of the cycle, which is as one would expect since the phases were generated around the time of bleeding. The one woman for whom menstruation did not show a significant phase effect had a good deal of breakthrough bleeding. It is also not surprising that there was a significant phase effect for oestrone in many cases (n=8), as changes in oestrone levels are largely a function of the 'liberating' effect of pill free interval, and the suppressive effect of the resumption of pill taking. The cell means of those women in whom the phase effect of oestrone did not achieve statistical significance indicate that either the magnitude of change was not great, or its timing was not consistent in both cycles.

Only three women prospectively confirmed cyclicity on the variable which they retrospectively reported to be their worst cyclical change in the MHRAQ-1. A further eight failed to confirm on their reported variable, but showed cyclicity for others, and five showed cyclicity when they had not previously reported experiencing any. Five of the women who had reported mood cyclicity only showed variations in phase for physical variables, but the opposite did not occur.

Table 3.05 Results of Individual ANOVA with Phases Aligned by Menstruation

Code Number	Self report Worst change	Individual ANOVA F Values: Menstruation Centred Phases							
		E-3-G	Mn	Ch	De	En	Fa	PC1	PC2
M1	n/a	2.30	**4.88***	0.55	0.87	0.34	0.33	0.32	0.90
M2	n/a	**24.37****	**6.85***	1.23	0.65	0.97	0.70	0.69	0.33
M4	moody	0.85	**20.59****	1.47	0.26	0.16	0.45	1.05	0.10
M5	de, ir	2.97	**217.98****	1.17	0.87	2.34	0.85	2.13	0.65
M6	n/a	0.36	**30.65****	1.17	**5.24***	1.26	**4.79***	1.96	2.63
M7	ir	**10.11****	**4.91***	0.48	1.38	3.55	0.35	1.11	2.93
M8	n/a	**9.82****	**78.50****	1.11	1.53	0.85	**4.09***	1.58	**7.77****
M9	n/a	1.67	0.86	1.80	0.74	1.48	0.75	2.53	1.12
M10	anger,bad skin	**9.70****	**14.45****	0.24	**3.90***	0.86	0.71	0.37	**7.10****
T1	did not say	2.89	**72.49****	2.03	2.09	0.53	1.63	0.82	1.58
T2	fatigue	2.18	**6.23***	1.76	1.51	1.48	0.32	1.42	1.14
T4	anger,upset	**23.80****	**15.71****	1.25	0.61	1.58	0.88	3.35	0.99
T6	moody	**5.06***	**77.48****	1.05	0.54	0.96	0.93	0.76	0.69
T7	de	**10.40****	**4.57***	0.66	0.46	0.20	0.61	0.36	1.69
T8	br, fatigue	**38.62****	**18.82****	2.61	0.97	**7.89****	**9.09****	2.54	2.42
T9	de, paranoia	2.19	**950.04****	1.09	0.71	1.20	1.48	1.88	0.78
T10	n/a	0.78	**36.55****	1.44	1.44	0.27	0.45	0.79	0.83
T11	de, ir, tearful	3.43	**25.6****	1.09	0.86	1.08	0.35	1.70	0.51

Key: E-3-G Oestrone, Mn-Bleeding, Ch-Cheerful & Happy, De-Depressed & Unhappy, En-Energetic & Active
Fa-Fatigued & Tired, PC1- Positive affect component, PC2- Negative affect component, Ir-Irritable
Ag-Aggressive, Tn-Tense & Anxious, Sw- Mood up and down, Cr-Creative, Re-Relaxed, Slf-Feeling good about self
Cnt-Lacking self control, Oth- Getting on well with others, Br-Breasts tender, Blt-Feeling bloated/Swollen
Ptp-Period type pain, Crv-Craving particular foods, Atr-Feeling sexually attractive, IS- Interest in sex
**- $p<0.01$, *- $p<0.05$

Table 3.05 - Continued

Code Number	Self report Worst change	Individual ANOVA F Values: Menstruation Centred Phases								
		Ir	Ag	Tn	Sw	Cr	Re	Slf	Cnt	Oth
M1	n/a	0.55	0.91	1.15	0.35	0.26	0.30	0.90	0.69	0.48
M2	n/a	0.18	0.39	0.39	0.55	0.09	0.33	0.86	0.57	0.54
M4	moody	0.38	0.44	0.69	0.69	0.65	0.35	0.46	1.00	**4.09***
M5	de, ir	0.82	1.00	0.72	0.79	0.97	1.40	0.64	0.72	1.64
M6	n/a	1.44	2.50	1.88	1.22	1.75	3.15	2.07	0.95	1.08
M7	ir	1.37	0.66	0.94	3.03	2.65	1.03	0.55	0.61	0.08
M8	n/a	**8.32****	1.00	0.56	1.68	1.27	3.52	1.72	**686.44****	3.28
M9	n/a	1.16	1.26	0.90	1.40	1.99	1.53	3.32	1.76	1.89
M10	anger,bad skin	**6.15***	**4.06***	2.14	1.87	1.20	0.98	0.37	0.33	0.22
T1	did not say	2.25	3.35	0.69	1.20	0.60	0.73	0.64	2.24	2.76
T2	fatigue	2.25	1.02	1.41	1.77	1.00	1.54	0.42	0.60	0.83
T4	anger,upset	0.75	**8.38***	0.59	0.73	3.14	2.23	**5.08***	1.30	**12.86****
T6	moody	0.43	0.44	0.86	1.03	0.40	0.58	0.48	1.25	1.19
T7	de	1.46	1.00	1.24	2.29	0.34	0.76	0.44	0.68	1.60
T8	br, fatigue	1.36	0.94	0.94	0.44	1.19	1.25	1.35	1.00	1.06
T9	de, paranoia	1.45	1.00	0.78	1.41	1.19	**4.77***	3.13	1.00	1.24
T10	n/a	0.59	0.40	1.80	1.30	1.34	1.52	2.37	0.54	1.04
T11	de, ir, tearful	0.60	0.46	0.25	0.71	1.25	0.72	1.07	1.01	0.66

Key: E-3-G Oestrone, Mn-Bleeding, Ch-Cheerful & Happy, De-Depressed & Unhappy, En-Energetic & Active
Fa-Fatigued & Tired, PC1- Positive affect component, PC2- Negative affect component, Ir-Irritable
Ag-Aggressive, Tn-Tense & Anxious, Sw- Mood up and down, Cr-Creative, Re-Relaxed, Slf-Feeling good about self
Cnt-Lacking self control, Oth- Getting on well with others, Br-Breasts tender, Blt-Feeling bloated/Swollen
Ptp-Period type pain, Crv-Craving particular foods, Atr-Feeling sexually attractive, IS- Interest in sex
**- $p<0.01$, *- $p<0.05$

Table 3.05 - Continued

Code Number	Self reported Worst Change	Individual ANOVA F Values:Menstruation Centred Phases					
		Br	Blt	Ptp	Crv	Atr	IS
M1	n/a	0.69	**81.77****	1.03	1.20	0.66	0.71
M2	n/a	**65.46****	n/a	n/a	n/a	0.31	0.17
M4	moody	0.97	2.70	0.84	0.51	**4.90***	**5.04***
M5	de, ir	0.96	**23.55****	**14.07****	0.96	2.32	1.90
M6	n/a	3.41	2.36	**9.64****	0.50	1.47	1.47
M7	ir	0.49	0.68	**4.7***	n/a	0.75	0.82
M8	n/a	1.00	1.74	3.83	0.83	0.90	1.14
M9	n/a	1.00	0.84	0.83	n/a	0.98	0.93
M10	anger,bad skin	0.64	2.54	0.91	0.80	2.05	0.64
T1	did not say	1.77	0.79	1.14	1.72	0.74	**5.68***
T2	fatigue	1.00	1.00	0.96	1.00	3.10	1.49
T4	anger,upset	2.78	1.34	0.92	0.69	0.83	1.46
T6	moody	1.00	0.99	**79.88****	0.85	0.56	0.52
T7	de	**11.66****	**7.33****	**27.24****	2.18	0.27	0.43
T8	br, fatigue	**14.52****	1.26	**9.00****	0.88	0.84	0.42
T9	de, paranoia	n/a	0.91	**4.45***	0.90	1.81	**19.12****
T10	n/a	0.69	**3.97***	**9.71****	0.58	1.27	1.00
T11	de, ir, tearful	**6.02***	2.79	1.91	0.58	1.87	2.89

Key: E-3-G Oestrone, Mn-Bleeding, Ch-Cheerful & Happy, De-Depressed & Unhappy, En-Energetic & Active
Fa-Fatigued & Tired, PC1- Positive affect component, PC2- Negative affect component, Ir-Irritable
Ag-Aggressive, Tn-Tense & Anxious, Sw- Mood up and down, Cr-Creative, Re-Relaxed, Slf-Feeling good al
Cnt-Lacking self control, Oth- Getting on well with others, Br-Breasts tender, Blt-Feeling bloated/Swollen
Ptp-Period type pain, Crv-Craving particular foods, Atr-Feeling sexually attractive, IS- Interest in sex
**- $p<0.01$, *- $p<0.05$

ANOVA tests were also carried out using the phased data, adjusted so that phases were centred around the time of the oestrogen peak. One cycle comprised the two phases before the peak-phase, the peak-phase itself, and the four phases after it. The peak was defined as the highest endogenous E-3-G value within eight days of a pfi: i.e.- phase 'Peak1-2', phase 'Peak1-1', phase 'Peak 1', phase 'Peak1+1', etc...., phase 'Peak1+4', followed by phase 'Peak2-2', etc.. Because the peak in oestrone did not occur in the same phase in both cycles, it was not a simple case of relabelling the phases to denote their relationship to the timing of the E-3-G peak. For a proportion of women the phases actually had to be redesignated, the effect of which was that some phases are duplicated or omitted for this analysis. This means that the time continuum has been broken, though for analytical purposes the two groups of 7 phases are considered hormonally analogous cycles.

ANOVA tests were conducted for positive and negative affect, E-3-G, the physical variables and the feeling sexually attractive scale. The results are summed up in Table 3.06 below in a similar manner to Table 3.05. Given that the data were aligned by oestrogen one would have expected an artifactually high frequency of significant phase effects for oestrogen. Curiously, only six women showed a significant phase effect of oestrogen, while eight did so in the bleed-centred analysis. On inspection of the cell means it is clear that in all but one case E-3-G is highest in the third phase, but the degree of change from one phase to the next does not necessarily achieve statistical significance.

Once again two women showed a significant phase effect for negative affect, but they were not the same women who showed an effect in the bleed-centred analysis. Only M7, who had a significant phase effect of negative affect, confirmed her reported worst change[6], and neither she nor T10 showed statistically significant change in E-3-G. On the physical side, no one showed a phase effect for food craving and only one woman each showed cyclicity by oestrogen phase in bloating and sexual attractiveness relative to the oestrogen peak. Three women had significant variation in breast tenderness and five in period pain.

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M7 was also one of the few women who had a greater than 30% reduction in PC2 according to the pre- to post- analysis.

Table 3.06 Results of Individual ANOVA with Phases Aligned by Oestrogen Peak

Code Number	Self reported Worst Change	Individual ANOVA F Values: Oestrogen Peak Centred Phases							
		E-3-G	Br	Blt	Ptp	Crv	Atr	PC1	PC2
M1	n/a	2.46	0.86	0.92	0.63	1.62	0.40	0.44	1.39
M2	n/a	**22.83****	0.94	n/a	n/a	n/a	0.33	0.86	0.46
M4	moody	0.92	1.08	2.70	0.84	0.60	**10.52****	2.40	0.15
M5	de, ir	1.02	1.46	0.71	0.77	0.78	0.17	0.25	0.15
M6	n/a	0.57	1.29	1.47	0.99	1.44	0.49	1.68	0.65
M7	ir	1.17	0.69	0.68	1.72	n/a	0.91	1.87	**5.97***
M8	n/a	**9.96****	0.94	1.72	3.83	0.83	2.03	2.10	1.98
M9	n/a	1.67	1.00	0.84	0.83	n/a	0.98	2.53	1.12
M10	anger,bad skin	1.17	0.87	0.98	0.91	1.11	1.43	0.84	0.82
T1	did not say	**4.59***	1.78	0.95	**4.59***	1.19	0.73	0.82	2.69
T2	fatigue	0.82	1.00	1.00	0.96	1.00	0.38	2.00	0.75
T4	anger,upset	**21.97****	**5.70***	1.94	1.08	0.77	0.92	2.71	0.97
T6	moody	**4.73***	1.00	0.95	**35.70****	0.71	0.73	1.01	0.84
T7	de	1.15	**8.50****	**10.17****	2.71	1.31	2.04	1.08	0.90
T8	br, fatigue	**47.98****	**21.32****	0.97	**9.00****	0.84	0.08	0.25	0.74
T9	de, paranoia	1.75	n/a	0.91	0.89	0.89	2.50	0.68	0.77
T10	n/a	0.83	0.92	1.90	0.77	0.75	1.83	2.05	**6.48***
T11	de, ir, tearful	1.78	2.20	1.61	**4.88***	0.60	1.18	1.89	0.72

Key: E-3-G Oestrone, Br-Breasts tender, Blt-Feeling bloated/Swollen, Ptp-Period type pain, Crv-Craving particular foods
Atr-Feeling sexually attractive, PC1- Positive affect component, PC2- Negative affect component

**- $p<0.01$, *- $p<0.05$

3.6.4.4 Detection of cyclical change in groups

A) Repeated measures ANOVA using PC's. Analysis of Variance for repeated measures was carried out on the six principle components for all women taken together (no phase transformation or standardization). There was no significant effect of daily mean E-3-G for the mood, sexuality or energy components (PC1- χ^2=22.930, p=0.689; PC2- χ^2=23.218, p=0.673, PC3- χ^2=36.436, p=0.106; PC6- χ^2=25.734, p=0.533). The physical components, however, did show a significant relationship to E-3-G level (PC4- χ^2=160.105, p=0.000; PC5- χ^2=89.345, p=0.000).

In addition to looking at the effect of the level of E-3-G, the influence of bleeding on the components was considered. Days when bleeding occurred were compared with days when it did not, also using E-3-G as a covariate in order to examine changes which could not be explained as a linear function of endogenous oestrogen concentration. Once again PCs 1, 2 and 6 did not show significant differences on the basis of bleeding (PC1- χ^2=0.007, p=0.936; PC2- χ^2=1.155, p=0.282; PC6- χ^2=0.980, p=0.322), while PCs 3, 4 and 5 did (PC3- χ^2=4.647, p=0.031; PC4- χ^2=114.992, p=0.00; PC5- χ^2=13.760, p=0.00). In other words, for all women taken together sexuality, bloating, period type pain, cravings, and breast tenderness seemed to be influenced by the presence or absence of bleeding.

Differences in component scores were also examined for the effects of pill type, pill day, self designated PMS status, and gynaecological age (no.yrs.from menarche). Only components 4 and 5 varied significantly by pill day (PC4- χ^2=176.091, p=0.00; PC5- χ^2=95.807, p=0.00), and no components differed significantly by pill type. This result is consistent with the previous finding for PCs 4 and 5, as the presence of bleeding is strongly influenced by day of the pill cycle. Analyses were carried out twice for the effect of retrospective PMS status: once where "maybe" was taken to mean "yes", and once where it was taken to mean "no". None of the components were statistically significant by PMS status; however, PC2, the negative affect component, had a value of χ^2=3.368, p=0.052 when "maybe" was taken as "yes". This is the component that one would expect to be the best distinguisher of PMS status.

Finally an ANOVA was carried out to assess the effect of gynaecological age on the principle components. There is some evidence that reporting of PMS type changes is maximal in women who have been experiencing cycles uninterrupted by pregnancy or steroid hormone use for between three and six years (Warner and Bancroft, 1990). It

was hypothesized that gynaecologically older women would have more cyclicity. Although seven years is the suggested time taken to achieve gynaecological maturity (Metcalf & MacKenzie, 1980), five years created a better split in the data set. The results were very similar to those for PMS status. No component was significantly different between the two groups, but again the statistic for PC2 was approaching significance (χ^2=3.123, p=0.066), with more negative affect in the gynaecologically "immature" group (less than 5 yrs. from menarche).

B) Multivariate analysis of variance (MANOVA). There is an overall suggestion in the above analyses that the volunteers tended to experience cyclical changes in their physical well being, and may in a few cases have experienced cyclical changes in their emotional well being as summarized in the negative affect variable. In order to test further this possibility, and to equate the likelihood of such experience with parameters of endogenous oestrogen change individual data were grouped in a number of ways. Four different groupings were generated on the basis of distinct aspects of oestrogen dynamics. The profiles of E-3-G are described in section 3.6.4 above. There are a number of ways in which the hormone data can be divided into groupings with potential biological meaning. In order to test the hypothesis that there is a relationship between residual ovarian function and subjective state one must question which aspects of oestrogen dynamics are indicative of function.

Since both the level of oestrogen and the speed of it's rise are potentially important indicators of function, four groupings for the MANOVA were designated by the following: 1) The **peak** level of E-3-G reached in the eight days following the onset of withdrawal bleeding for both cycles. The *high* group had peaks of ≥30ng/gr (n=7), while the *low* group had <30ng/gr (n=10). M9 was excluded because her two cycles were different. 2) The **baseline** level of E-3-G, which was determined by taking the mean of pill days 15 to 21. There were *low, intermediate, and high* baseline groups, with mean levels of 8.8ng/gr (n=5), 12.3ng/gr (n=8), and 16.1ng/gr (n=5) respectively. 3) The **rise** in the level of E-3-G from baseline to peak, or whether or not the peak was at least double the baseline level. In the *doubling* group E-3-G changed by at least two times from the baseline to the peak in both cycles (n=11), whereas it was less than double in one or both cycles in the *non-doubling* group. And 4) The **symmetry** of the E-3-G profiles for the two cycles, or whether or not the rise from baseline to peak was equal in the two cycles. If the ratio of change between the

baseline and peak for both cycles was ≥1 they were *symmetrical* (n=8), but if it was <1 they were *not symmetrical* (n=10).

'Group' was a two level variable, except for the 'baseline' group which had three levels. 'Cycle' was a two, and 'phase' a seven level variable. The phases were oestrogen-peak-centred. The variables studied included breast tenderness, bloating, period type pain, food cravings, feeling sexually attractive, and positive and negative affect. These met the symmetry conditions in some instances and not others. Breast tenderness, bloating, and period pain were not homogeneous. Food craving was not homogeneous in three groupings, but was in the 'symmetry' groups. Feeling sexually attractive, and positive and negative affect were all homogeneous at the 1% level of the test. Only negative affect was always spherical. Breast tenderness, bloating, and period pain were never spherical, and food craving and feeling sexually attractive sometimes.

Four *post hoc* contrasts were carried out on each variable in each hormone grouping to examine the nature of the phase relationships. They were as follows: 1) a comparison of the phase when E-3-G peaked (Phase 3) with all the others phases; 2) a comparison of the phase when E-3-G peaked (Phase 3) with all the others, excluding the main menstrual phase (Phase 1); 3) a comparison of the three phases in which E-3-G rose (Phase 2), peaked (Phase 3), and fell (Phase 4), and was therefore changing, with the other four "baseline" phases; 4) a comparison of the two menstrual phases (Phase 1&2) with the peak E-3-G phase (Phase 3), excluding all other phases. The results are summarized in Tables 3.07 to 3.10, and each variable is considered in turn.

i) Breast tenderness. There was no effect of group on breast tenderness for any of the hormone parameters. This initial, univariate, between-subject test is an overall measure of group differences, but does not take account of any interactions. In the 'baseline' and the 'rise' groups the cycles were significantly different, (p=.03, and p=.04), and in the 'rise' group, the group by cycle interaction approached significance (p=.07). Neither of these groupings were based on similarity between cycles, while the 'peak' and 'symmetry' groups were, so this result is not surprising.

The multivariate tests for the effects of phase, and group by phase were significant for the 'peak' group only (p=.04, .03). This suggests that the phases were different from each other overall, and also between groups for breast tenderness. Indeed, this was the

Table 3.07 MANOVA Results for "Peak" Oestrogen Grouping

Test Statistic	Br	Blt	Ptp	Crv	Atr	PC1	PC2
Sphericity tests	0.00	0.00	0.00	0.00	0.00	0.83	0.85
	0.00	0.00	0.00	0.15	0.28	0.17	0.49
Homogeneity test	N	N	N	Y	Y	Y	Y
Between subjects effects							
Constant	**12.99****	**23.08****	**13.83****	**9.28****	**71.39****	0.05	0.03
Peak	1.21	4.28	1.24	0.54	0.51	0.18	1.53
Within subject effects							
Cycle	3.22	0.63	0.03	**5.27***	0.93	0.09	0.92
Peak x cycle	0.00	0.01	1.83	1.34	1.92	0.00	1.06
Multivariate tests							
Peak x phase	**3.88***	0.23	1.31	1.10	0.74	2.01	0.53
Phase	**3.68***	1.84	2.11	0.63	0.91	0.42	1.79
Average tests							
Phase	**6.81****	**5.86****	**4.55****	1.60	0.53	0.50	**2.55***
Peak x phase	2.03	0.41	0.98	0.77	0.26	0.64	0.26
P.h. test 1: Phase t=	-1.78	0.36	1.32	-1.00	-0.14	-0.43	-1.28
P.h. test 1: Pk x Phs t=	1.20	0.32	-0.32	2.11	0.09	-0.51	0.69
P.h. test 2: Phase t=	**2.96***	**3.15****	**3.44****	0.38	-1.43	-0.99	2.11
P.h. test 2: Pk x Phs t=	-1.44	-0.74	-0.80	-1.01	-0.10	-0.51	-0.52
P.h. test 3: Phase t=	**-2.57***	**-2.27***	0.55	-0.67	0.25	0.07	-1.35
P.h. test 3: Pk x Phs t=	0.61	0.98	-0.51	1.57	0.24	-0.14	-0.24
P.h. test 4: Phase t=	**-2.45***	-1.15	-0.71	-1.47	0.55	0.24	-1.15
P.h. test 4: Pk x Phs t=	0.44	0.37	-0.51	0.19	-0.93	-0.40	0.01
Multivariate tests							
Peak x cycle x phase	1.01	1.01	1.92	0.24	0.51	0.53	0.55
Cycle x phase	2.07	1.01	0.50	0.69	0.44	1.63	0.84
Average tests							
Cycle x phase	1.37	0.71	1.44	1.40	0.73	1.63	0.95
Peak x cycle x phase	1.14	**2.91***	0.78	0.12	0.93	0.69	0.68
P.h. test 1: Cy x Phs t=	1.24	-1.20	1.25	1.55	-0.91	0.53	-0.15
P.h. test 1: PkxCxPh t=	0.00	-1.51	-1.30	0.04	-1.03	-0.54	0.24
P.h. test 2: Cy x Phs t=	0.25	-0.54	-0.69	1.54	1.41	0.60	-0.39
P.h. test 2: PkxCxPh t=	-1.04	0.36	-0.45	-0.03	1.46	0.45	0.47
P.h. test 3: Cy x Phs t=	0.22	-0.42	1.28	-1.04	0.65	2.00	-1.53
P.h. test 3: PkxCxPh t=	-0.58	-1.12	-1.04	0.55	1.02	1.19	-1.76
P.h. test 4: Cy x Phs t=	-1.83	1.33	-0.09	-0.46	-0.06	-1.72	2.10
P.h. test 4: PkxCxPh t=	0.74	2.16	0.03	0.37	-0.36	-1.15	0.92

Key: Br- Breast tenderness, Blt- Bloating, Ptp- Period type pain, Crv- Food craving, Atr- Feeling sexually attractive, PC1- Positive affect, PC2- Negative affect, P.h.- Post hoc test, C/y- Cycle, Ph/s- Phase, Pk- Peak

Table 3.08 MANOVA Results for Oestrogen "Rise" Grouping

Test Statistic	Br	Blt	Ptp	Crv	Atr	PC1	PC2
Sphericity tests	0.00	0.00	0.00	0.00	0.02	0.00	0.15
	0.00	0.00	0.00	0.14	0.27	0.06	0.46
Homogeneity test	N	N	N	Y	Y	Y	Y
Between subjects effects							
Constant	**11.71****	**21.71****	**13.32****	**9.29****	**75.75****	0.04	0.11
Rise	0.53	0.21	0.02	0.04	0.47	0.07	0.22
Within subject effects							
Cycle	5.35*	0.03	0.66	**3.73***	0.09	0.44	1.42
Rise x cycle	3.78	0.02	0.22	0.60	0.56	1.01	0.21
Multivariate tests							
Rise x phase	0.53	1.18	0.57	0.24	0.81	1.03	2.46
Phase	1.81	1.95	1.55	0.64	1.01	0.58	1.39
Average tests							
Phase	**6.24****	**4.43****	**3.19****	1.47	0.52	0.44	1.93
Rise x phase	1.48	0.71	1.42	0.27	0.89	2.07	**2.84***
P.h. test 1: Phase t=	-1.71	-0.40	1.00	-0.99	-0.19	-1.02	-0.44
P.h. test 1: Rise x Phs t=	-1.18	-1.09	-1.63	-0.74	0.40	1.21	-0.92
P.h. test 2: Phase t=	**2.82***	2.11	1.09	0.40	-0.95	-0.17	1.15
P.h. test 2: Rise x Phs t=	1.49	-0.58	-0.78	0.49	1.21	1.48	**-2.23***
P.h. test 3: Phase t=	**-2.49***	**-2.53***	0.24	-0.82	0.38	0.23	-1.57
P.h. test 3: Rise x Phs t=	-1.12	-0.49	-1.74	0.15	-1.14	-1.82	0.56
P.h. test 4: Phase t=	**-2.37***	-1.40	-0.71	-1.46	0.49	0.15	-1.75
P.h. test 4: Rise x Phs t=	-1.51	-0.69	-1.01	-0.10	-0.89	-1.66	2.04
Multivariate tests							
Rise x cycle x phase	0.91	1.73	0.92	0.53	0.62	0.90	0.24
Cycle x phase	1.85	1.04	0.64	0.64	0.34	1.67	0.98
Average tests							
Cycle x phase	1.67	1.05	1.31	1.13	0.58	1.04	1.19
Rise x cycle x phase	1.75	0.81	1.33	1.17	1.04	0.77	0.26
P.h. test 1: Cy x Phs t=	1.05	-1.37	0.95	1.37	-0.43	0.27	-0.04
P.h. test 1: RisexCxPh t=	1.81	-0.02	-1.12	2.07	0.25	0.12	0.19
P.h. test 2: Cy x Phs t=	0.51	-0.99	-0.95	1.40	1.09	0.68	-1.03
P.h. test 2: RisexCxPh t=	-0.85	-1.00	-1.03	1.16	1.53	0.37	-0.11
P.h. test 3: Cy x Phs t=	-0.06	-0.96	0.81	-1.11	0.54	2.01	-1.63
P.h. test 3: RisexCxPh t=	**2.32***	1.40	-0.58	0.11	-0.60	0.56	0.38
P.h. test 4: Cy x Phs t=	**-2.64***	0.50	-0.59	-0.47	0.57	-0.74	1.72
P.h. test 4: RisexCxPh t=	**2.50***	0.44	1.73	-0.21	-1.23	-0.77	-0.63

Key: Br- Breast tenderness, Blt- Bloating, Ptp- Period type pain, Crv- Food craving, Atr- Feeling sexually attractive, PC1- Positive affect, PC2- Negative affect, P.h.- Post hoc test, C/y- Cycle, Ph/s- Phase

Table 3.09 MANOVA Results for Oestrogen "Baseline" Grouping

Test Statistic	Br	Blt	Ptp	Crv	Atr	PC1	PC2
Sphericity tests	0.00	0.00	0.00	0.00	0.03	0.00	0.08
	0.00	0.00	0.00	0.05	0.21	0.05	0.10
Homogeneity test	N	N	N	Y	Y	Y	Y
Between subjects effects							
Constant	**13.78****	**22.19****	**12.71****	**14.69****	**79.66****	0.01	0.72
Baseline	1.22	0.18	0.01	3.20	1.03	0.29	**6.63****
Within subject effects							
Cycle	**5.53***	0.12	1.42	4.54	0.22	0.20	1.10
Baseline x cycle	2.70	0.85	1.86	0.30	0.21	0.40	0.86
Multivariate tests							
Baseline x phase	0.79	0.54	1.55	1.34	1.38	1.72	0.97
Phase	0.19	1.44	2.08	0.62	1.74	0.71	1.57
Average tests							
Phase	**6.50****	**4.33****	**2.83***	1.99	0.53	0.52	1.29
Baseline x phase	0.78	0.67	1.75	1.03	1.43	0.91	0.96
P.h. test 1: Phase t=	-1.68	-0.84	0.71	-1.43	0.00	-0.99	-0.55
P.h. test 1: Bsln x Phs t=	-1.18	1.29	0.14	1.37	-0.96	1.27	-0.24
P.h. test 1: Bsln x Phs t=	0.36	0.99	1.87	-1.98	-1.39	-0.32	-0.84
P.h. test 2: Phase t=	**3.02****	1.94	0.85	0.59	-0.67	0.23	0.62
P.h. test 2: Bsln x Phs t=	0.34	0.05	1.22	-0.37	-0.13	-0.97	0.27
P.h. test 2: Bsln x Phs t=	1.37	0.50	1.02	1.86	-0.51	-0.14	1.00
P.h. test 3: Phase t=	**-2.43***	**-2.67***	-0.04	-0.72	0.31	-0.18	-1.59
P.h. test 3: Bsln x Phs t=	-0.76	0.17	-0.13	-0.67	-0.76	0.66	0.38
P.h. test 3: Bsln x Phs t=	0.38	0.94	1.52	-0.89	1.74	0.94	-1.52
P.h. test 4: Phase t=	**-2.35***	-1.51	-0.67	-1.66	0.21	-0.27	-1.27
P.h. test 4: Bsln x Phs t=	-0.46	0.01	-1.72	1.05	0.86	0.91	0.47
P.h. test 4: Bsln x Phs t=	-0.24	0.83	1.64	-0.95	0.79	0.38	-0.13
Multivariate tests							
Baseline x cycle x phase	1.42	0.99	1.11	0.69	0.39	0.68	1.42
Cycle x phase	3.24	0.82	0.60	0.79	0.32	1.49	1.58
Average tests							
Cycle x phase	**2.28***	1.41	1.22	1.41	0.69	1.08	1.35
Baseline x cycle x phase	1.78	0.87	0.89	0.39	0.33	0.40	1.22
P.h. test 1: Cy x Phs t=	1.11	-1.62	0.61	1.58	-0.22	0.40	0.01
P.h. test 1: BslnxCxPh t=	0.87	0.87	0.92	-0.36	-1.06	-0.69	-0.15
P.h. test 1: BslnxCxPh t=	0.01	0.99	0.61	0.88	0.00	0.48	0.28
P.h. test 2: Cy x Phs t=	0.57	-1.35	-1.18	1.59	1.15	0.70	-1.08
P.h. test 2: BslnxCxPh t=	-1.32	1.24	0.30	-0.21	0.79	0.10	0.10
P.h. test 2: BslnxCxPh t=	0.81	-0.46	1.06	1.09	-0.94	0.05	1.00
P.h. test 3: Cy x Phs t=	0.10	-0.83	0.52	-1.21	0.39	1.99	-1.49
P.h. test 3: BslnxCxPh t=	1.42	0.36	1.40	0.77	0.16	0.39	-0.11
P.h. test 3: BslnxCxPh t=	0.50	1.96	-0.07	0.07	0.22	-0.65	0.23
P.h. test 4: Cy x Phs t=	**-2.46***	0.41	-0.32	-0.45	0.33	-0.83	1.51
P.h. test 4: BslnxCxPh t=	**2.27***	1.09	0.39	-0.25	0.03	-0.09	0.27
P.h. test 4: BslnxCxPh t=	-1.38	-0.14	0.42	-0.25	0.29	-0.43	0.05

Key: Br- Breast tenderness, Blt- Bloating, Ptp- Period type pain, Crv- Food craving, Atr- Feeling sexually attractive, PC1- Positive affect, PC2- Negative affect, P.h.- Post hoc test, C/y- Cycle, Ph/s- Phase, Bsln- Baseline

Table 3.10 MANOVA Results for Oestrogen "Symmetry" Grouping

Test Statistic	Br	Blt	Ptp	Crv	Atr	PC1	PC2
Sphericity tests	0.00	0.00	0.00	0.00	0.02	0.00	0.06
	0.00	0.00	0.00	0.04	0.22	0.04	0.37
Homogeneity test	N	N	N	Y	Y	Y	Y
Between subjects effects							
Constant	**12.24****	**21.72****	**13.00****	**8.72****	**101.19****	0.14	0.01
Symmetry	2.66	0.48	0.45	2.03	**7.01***	1.50	0.97
Within subject effects							
Cycle	3.23	0.27	1.33	3.93	0.39	0.15	0.19
Symmetry x cycle	0.04	2.85	1.54	0.08	1.14	0.21	0.25
Multivariate tests							
Symmetry x phase	1.28	2.31	1.01	1.54	0.65	0.66	1.54
Phase	2.38	1.46	1.36	0.58	1.29	0.60	1.41
Average tests							
Phase	**6.09****	**4.16****	**2.37***	1.28	0.53	0.57	1.10
Symmetry x phase	1.34	1.46	**2.61***	1.83	0.84	0.75	1.19
P.h. test 1: Phase t=	-1.76	-0.93	0.41	-1.01	0.07	-0.96	-0.40
P.h. test 1: Sym x Phs t=	0.46	-1.75	-1.70	0.57	1.15	-0.94	1.21
P.h. test 2: Phase t=	**2.79***	1.87	0.69	0.29	-0.69	0.21	0.52
P.h. test 2: Sym x Phs t=	-1.07	-1.11	-2.07	-1.27	0.08	0.73	-0.81
P.h. test 3: Phase t=	**-2.49***	**-2.67***	-0.26	-0.76	0.42	0.09	-1.40
P.h. test 3: Sym x Phs t=	1.02	-0.35	-1.13	0.16	1.34	1.00	0.36
P.h. test 4: Phase t=	**-2.36***	-1.34	-0.78	-1.32	0.42	-0.25	-1.14
P.h. test 4: Sym x Phs t=	0.86	1.67	0.51	1.44	0.52	-0.71	0.50
Multivariate tests							
Symmetry x cycle x phase	1.26	0.25	1.38	2.16	1.33	1.32	0.54
Cycle x phase	1.65	1.00	0.64	0.71	0.79	2.53	0.96
Average tests							
Cycle x phase	1.33	1.36	1.39	1.25	1.08	1.47	1.26
Symmetry x cycle x phase	0.40	0.39	0.80	1.49	1.53	0.90	0.37
P.h. test 1: Cy x Phs t=	1.14	-1.50	0.58	1.37	-0.29	0.43	-0.12
P.h. test 1: SymxCxPh t=	-0.67	-0.60	-0.89	-2.16	0.54	0.72	-0.63
P.h. test 2: Cy x Phs t=	0.67	-1.13	-1.34	1.59	1.65	1.03	-1.17
P.h. test 2: SymxCxPh t=	1.62	0.01	-1.13	0.27	1.59	1.37	-0.60
P.h. test 3: Cy x Phs t=	0.24	-0.91	0.59	-0.91	0.52	2.41	-1.67
P.h. test 3: SymxCxPh t=	-0.29	-1.17	-0.72	1.36	0.49	1.23	-0.56
P.h. test 4: Cy x Phs t=	-1.80	0.46	-0.46	-0.65	0.34	-0.73	1.47
P.h. test 4: SymxCxPh t=	0.31	-0.65	-1.07	-0.74	0.00	0.85	-0.92

Key: Br- Breast tenderness, Blt- Bloating, Ptp- Period type pain, Crv- Food craving, Atr- Feeling sexually attractive, PC1- Positive affect, PC2- Negative affect, P.h.- Post hoc test, C/y- Cycle, Ph/s- Phase, Sym- Symmetry

only instance, for any variable, for any grouping of women in which the multivariate tests were significant. Multivariate tests that were performed for cycle by phase, and group by cycle by phase interactions were never significant. Inspection of the epsilon adjusted univariate statistics revealed that the phases were significantly different at the 1% level in all four hormonal groupings, but there is no group by phase, cycle by phase, or group by cycle by phase interaction.

For breast tenderness, the second, third, and fourth *post hoc* tests were all significant (at the p=.05 level or less) in all four hormone determined groupings. Indicating that no matter which parameter was used to classify groups of women breast tenderness still showed significant differences over the phases of the cycle in relation to E-3-G.

The amount of breast tenderness was different in the two 'peak' groups. Women whose endogenous oestrogen was more suppressed and in whom E-3-G levels never reached peaks of ≥30µg/gr crt. had more breast tenderness than the *high* oestrogen group. In both groups breast tenderness appeared to be inversely related to the level of E-3-G, with least breast tenderness when oestrogen was highest. So, the phase relationship to the oestrogen peak was similar, but the *low* oestrogen group were more severely affected. Figure 3.10 shows the difference in mean breast tenderness scores for the two groups over the oestrogen centred phases.

ii) Bloating. In the 'peak' group there was a near significant effect of group in the between-subject univariate test (p=.06) for bloating, but there was no significant effect of any other hormonal grouping. The cycles were not significantly different in any of the groupings, nor was there any interaction between group and cycle. As stated above none of the multivariate tests were significant for any group.

The epsilon adjusted univariate test of phase effect, however, was significant in all groupings; at the 1% level in the 'peak', 'baseline', and 'rise' groups, and at the 5% level in the symmetry groups. In all hormonal four groupings, the third *post hoc* test, which estimated the difference between the phases of changing oestrogen with the baseline level, was significant ('peak'- p=.04, 'baseline', 'rise', 'symmetry'- p=.02). In the 'peak' groups the second test was also significant (p=.01), but only approached significance in the other three groupings.

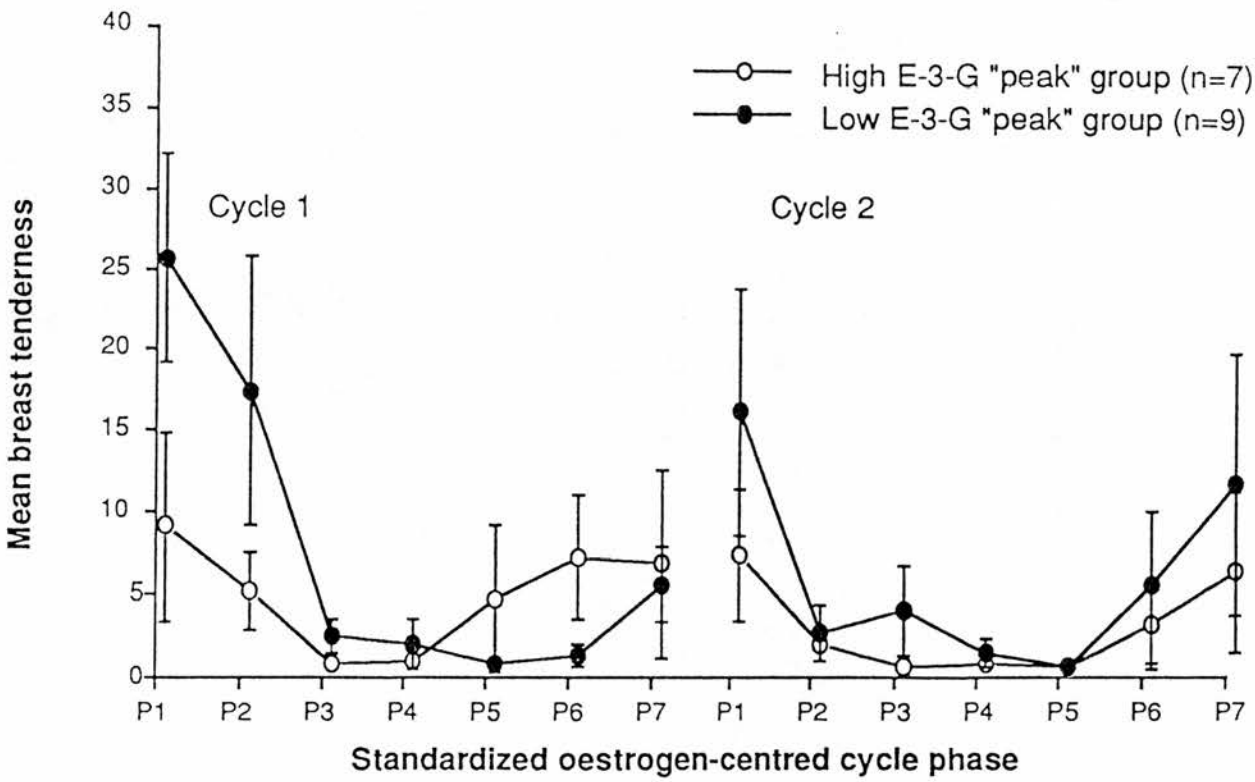

Figure 3.10 Oestrogen-centred phase means for the high and low oestrogen "peak" groups for breast tenderness.

Further, the 'peak' by cycle by phase interaction was significant at the 5% level. So when cycle and phase are both taken into account, the *high* and *low* oestrogen groups seem to experience different amounts of bloating. As was the case for breast tenderness, the cell means indicate that women with lower peak levels of E-3-G had more pronounced bloating (see Figure 3.11). None of the other oestrogen parameters distinguished between groups.

iii) Period Pain. The between-subject univariate test for the effect of group was not significant for any hormonal grouping, nor were there any significant within subject effects. The multivariate tests were not significant. The only significant results for period pain were the epsilon-adjusted, univariate tests of phase effect. In the 'peak', 'baseline', and 'rise' groups this test was significant at the 5% level, but it only approached significance in the 'symmetry' group. The only *post hoc* test that was significant for period pain was the second one, in the 'peak' grouping: i.e. the highest oestrogen phase was different from all the others (p=.01) when the first "menstrual" phase was excluded.

iv) Food Craving. There was a significant, or nearly significant within-subject effect of cycle for food craving in all the groupings: 'peak' p=.04, 'baseline' p=.05, 'rise' p=.07, 'symmetry' p=.07. Thus the first and second cycle of the study were different from each other, no matter which oestrogen parameter was used to group the data. This presumably obscured any potential phase effect in the data and none of the other tests carried out achieved significance.

v) Feeling Sexually Attractive. Only one test was significant for this variable. In the 'symmetry' grouping the initial between-subject univariate test was significant (p=.02). This group difference was not confirmed, however, by the more powerful multivariate, or epsilon-adjusted univariate tests. An inspection of the cell means reveals that the group of women whose cycles were more symmetrical had higher self-reported feelings of sexual attractiveness. That is, the women in whom E-3-G changed by an equivalent amount between the baseline and peak levels in both study cycles, reported feeling more sexually attractive (see Figure 3.12).

vi) Positive Affect. No tests were significant for positive affect, the measure of positive affect. So, there were no differences between phases, cycles, or groups for any of the hormone parameters investigated (see Tables 3.07-3.10).

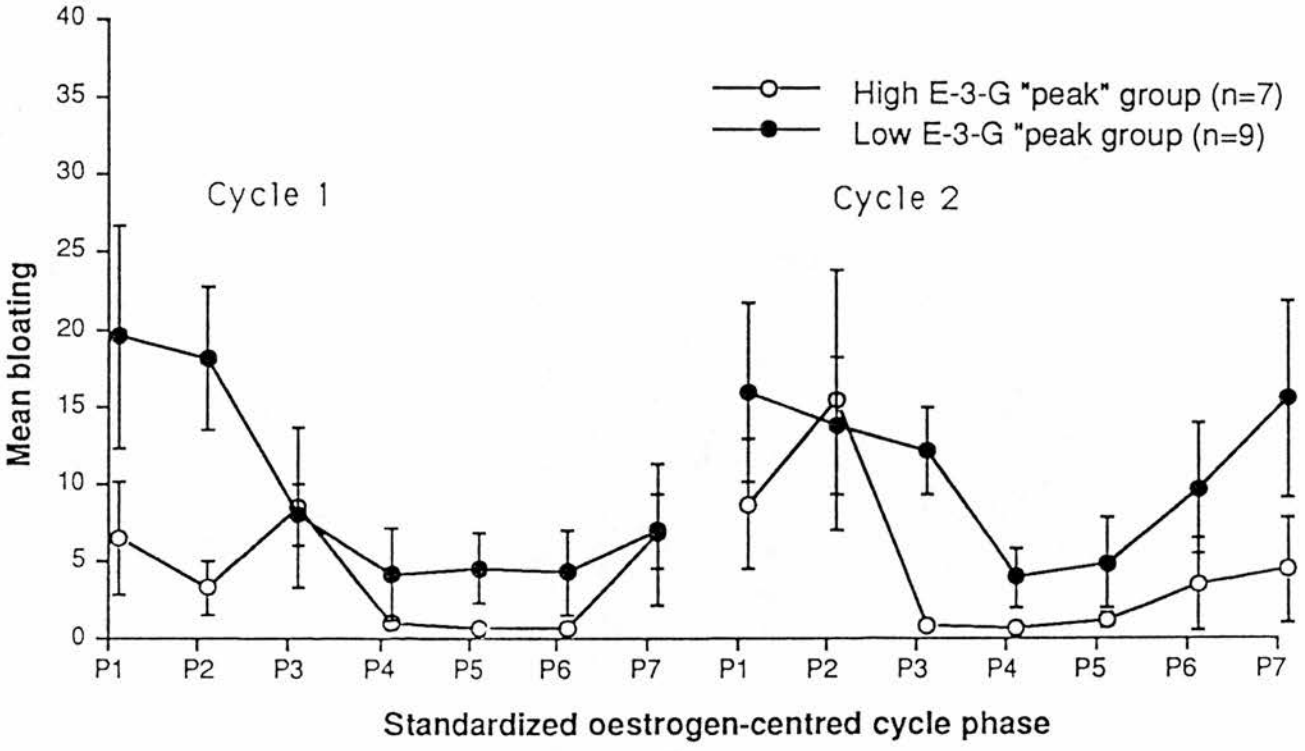

Figure 3.11 Oestrogen-centred phase means for the high and low oestrogen "peak" groups for bloating

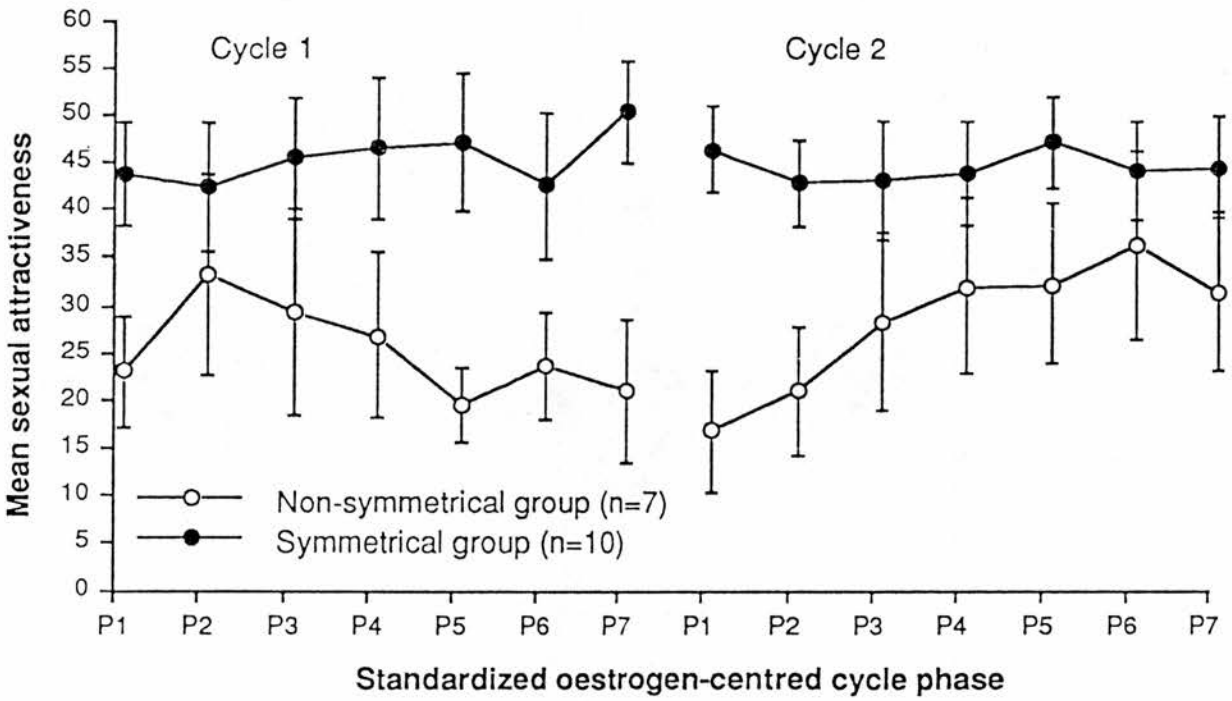

Figure 3.12 Comparison of oestrogen-centred phase means for sexual attractiveness in those women who had similar oestrogen profiles in two consecutive cycles and those who did not.

vii) Negative affect. The results for negative affect were not as consistent as for the other variables. Results seemed to differ according to the hormonal parameter under investigation. No test was significant for the 'symmetry' grouping. In the 'peak' group, only the univariate test of phase effect was significant (p=.03). (No adjustment by the epsilon value was needed in the case of univariate tests for negative affect, as data were spherical in all the groupings, due to the use of standard *z* scores.) The 'peak' groups and cycles did not differ, and none of the *post hoc* tests were significant.

In the 'rise' group, the univariate test of phase effect was not significant at p=.09, but the group by phase test was, at p=.02, indicating that the groups were different when the interaction effect of phase was accounted for. Only the second *post hoc* test, was significant (p=.05), indicating that phase 3 was different from all the others when the menstrual phase was excluded.

Finally, in the 'baseline' grouping there was a significant difference between the groups in the between-subjects univariate test (p=.01). The cell means show that the *intermediate* 'baseline' group had lower scores for negative affect in all phases than either the *high* or *low* groups. The *intermediate* 'baseline' group tended to show more clearly cyclical patterns of E-3-G, rising and falling in response to the pill free interval,than the other two groups. In the univariate ANOVA aligned by bleeding discussed above, the individuals in the *high* and *low* 'baseline' groups had less cyclical profiles of E-3-G, with only two out of ten showing a significant phase effect for oestrogen, versus five out of eight in the *intermediate* group. The 'baseline' group differences in negative affect are shown in Figure 3.13.

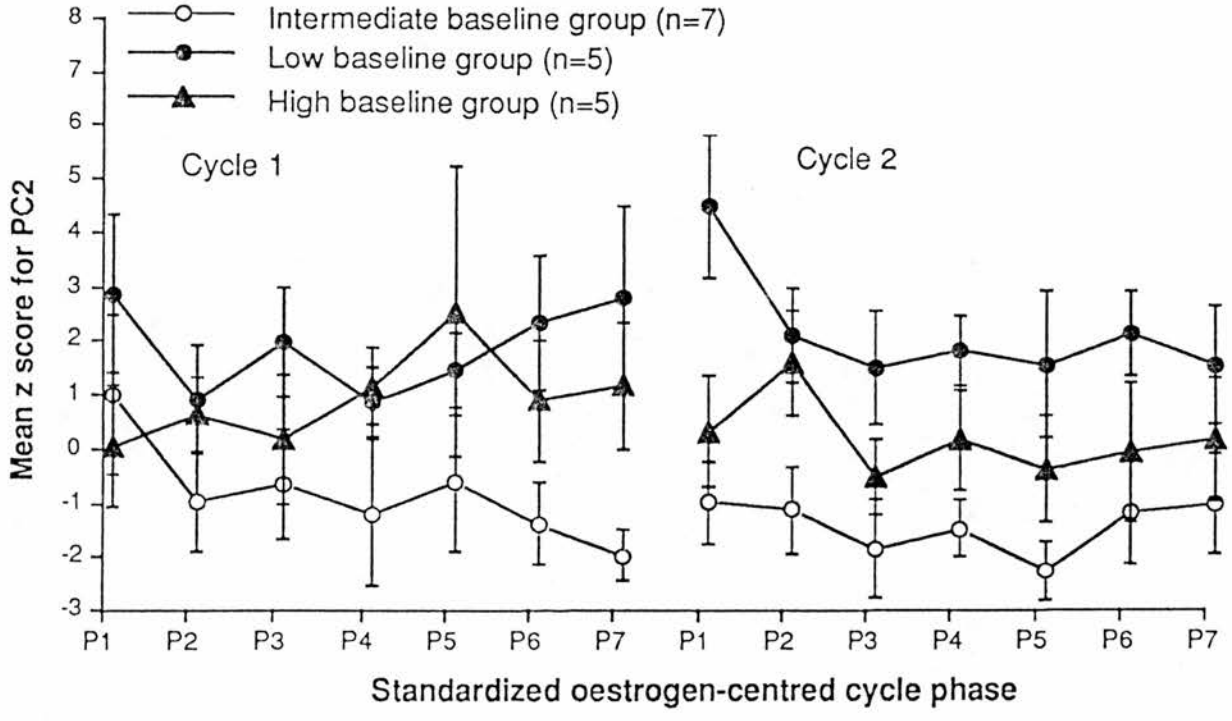

Figure 3.13 Comparison of oestrogen-centred phase means for negative affect in women with high, intermediate, and low baseline levels of oestrogen.

3.7 Summary and Conclusions

This study was concerned with relating cyclical change in subjectively reported well being to residual ovarian steroid production in two different groups of pill users. The observational, correlational design was directed at accounting for one possible mechanism which might explain the persistence of such experience in pill takers.

3.7.1 The Representativeness of the Sample

All those who completed the study were white, middle class, employed, highly motivated, and well educated. All women were in relationships, the majority permanent, and were largely non-religious, nulliparous, and well established on the pill. They are therefore a homogeneous and non-representative sample of the population at large. Nevertheless, they are similar to the majority of FPC attenders (see Chapter Four).

3.7.2 Evidence of Residual Ovarian Function

The first aim of this investigation was to establish whether or not there is continued ovarian function during OC cycles. All 20 women showed some evidence of residual ovarian function determined by urinary hormone analysis[7]. As expected from previous reports the majority of endogenous oestrogen change was concentrated during and immediately after the pfi, while progesterone levels remained basal at all times. E-3-G profiles were largely consistent within women over time[8]. Contrary to expectation women established on monophasic and triphasic pills showed similar amounts and dynamics of oestrone production[9].

7
There was also evidence of folliculogenesis from ultrasound scanning and serum hormone measures of half of the monophasic takers.

8
Serum levels were equivalent in a subsequent scanning cycle.

9
Gonadotrophin levels during a scanning cycle seemed to return to normal and produce follicle growth in a subgroup of monophasic takers, in agreement with previous reports (van der Spuy et al., 1990). Unfortunately, it was not possible to compare follicular growth in triphasic and monophasic takers. In fact, a disproportionate number of triphasic takers had stopped taking the pill by the time scanning was carried out (7 out of 10 vs. 3 out of 10 monos.). In such a small sample of women it is difficult to know if this reflects some adverse effect of the formulation or difference in the sort of woman who uses triphasics, or is simply a function of the particular women who took part. It has been suggested, but not shown definitively that triphasic takers may experience

The picture of ovarian function found in this study is similar to previous reports which indicate that for most women oestrogen levels are very low and may show a transient rise beginning in the pfi, but are still generally lower than at the equivalent phase of the normal cycle (early follicular). It is difficult to know if the subtle alterations in steroid levels which most women showed are of any clinical consequence. It is more likely that observed differences in endogenous steroid levels actually reflect differences in the rate of pill metabolism. The implications of inter-individual differences in steroid metabolism are not known, and there was wide variation in the degree of release from pill suppression across women. One woman on each pill type showed a sustained and marked rise in E-3-G during monitoring, and one woman who showed only moderate E-3-G became pregnant while regularly taking Trinordiol a few months after the end of the study. There was even more marked evidence of residual ovarian function amongst women taking the monophasic formulation, Marvelon, in a subsequent study which is described fully in Chapter Six.

3.7.3 Evidence of Cyclical Change in Subjective State

The second aim of this investigation was to determine whether or not the sample experienced cyclical change in their emotional and physical well being. A variety of methods were used to establish the presence of cyclicity in individuals and they produced complex and inconsistent results. Retrospectively, 13 out of 20 (65%) of the women said that they thought they had or might have PMS. However, using the '30% change' rule very few women in this sample confirmed the existence of PMS. Only four women met the NIMH criterion for PMS for at least one physical change over two prospectively monitored cycles (M6, T7, T8 & T10), while two other women met it for mood changes (M7 & T11).

Few women had consistent experiences during both cycles. However, 15 out of 18 women had a significant reduction in one or more physical 'symptom/s' during at least one cycle. More than half of these individuals had used less than 30% of the range of the VAS. Fifteen women also had at least a 30% change in their standard score *z* for

---

more adverse mood reactions when commencing the pill than monophasic takers (Bancroft et al., 1987a). Another possibility is that women chose to take part in this investigation because they already had reservations about the pill and used the study as an opportunity for a close reading of cycle-related events in order to confirm pre-existent attributions.

for positive and negative affect. These were not necessarily the same women who had shown physical change, and the change in mood was not necessarily in the expected direction. For example in 8 of the 15 cycles where positive affect changed women were *less* happy after the bleed. In the majority of cases negative mood was lower after bleeding, although in 3 cycles out of 14 women were still unhappy after a bleed. Women were somewhat more likely to experience two physically similar cycles, and all physical symptoms appeared prior to bleeding and remitted or improved after bleeding finished. The low level of symptom experience in this sample is not particularly surprising as volunteers were not selected on the basis of PMS reporting. Pill use may also be reducing cyclicity for at least a portion (eg. Woods, et al., 1982).

ANOVA was carried out to determine whether or not individuals showed significant change in well being over all of the cycles phases with consistent timing in relation to either bleeding or the peak level of E-3-G. More women showed significant phase effects for individual mood variables, or PC's 1 and 2 in relation to bleeding than peak oestrogen. Physical variables changed in relation to oestrogen, but more often in relation to bleeding. Cyclicity in well being was generally subtle and varied a great deal both across and within individuals.

Triphasic pills are meant to produce fewer "side effects" than monophasics via lower dosage and perhaps because they emulate the menstrual cycle (eg. Hale, 1987). The concept that triphasics are "more natural" or "healthier" (Guillebaud, 1984) may mean that they are more often prescribed to women who are anxious about side effects, have experienced them on other formulations, or are otherwise ambivalent about taking the pill. These factors are likely to predispose them to discontinue. There was some broad support for the idea that triphasic takers are more anxious than monophasic takers in this investigation since they tended to report more PMS and to have higher neuroticism scores on the EPI. However, there was no indication that triphasic takers had different amounts or patterns of cyclical change.

3.7.4 Evidence of a Relationship Between Endogenous Oestrogen and Subjective State

The final aim of this research was to explore the link, if any, between the dynamics of endogenous steroids and subjective state over the OC cycle. When the rotated principle components were entered into 1-way ANOVA the physical variables were more closely

associated with levels of oestrogen than the mood variables. There was significant change in physical and sexuality components over the pill cycle in the whole sample which co-varied with E-3-G. It is likely that sexual feelings and activity are influenced by the timing of bleeding, with sexual activity considerably less likely to occur on bleeding days. Yet once bleeding has finished, the likelihood of sexual activity is probably not influenced by the day of the pill cycle. Equally it is not surprising to find an effect of cycle day and bleeding on the experience of bloating, breast tenderness, food craving and period type pain, as physical symptoms are not likely to occur at times distant from bleeding (Metcalf et al., 1990). It is also more likely that physical symptoms have a mechanistic relationship to physiological events than mood states (Bancroft & Backström, 1985). Perhaps, the absence of endogenous oestrogen which presumably reflects the potency of exogenous steroids at the end of the pill cycle, is responsible for physical symptoms at this time.

This analysis showed a near significant difference between women who retrospectively reported PMS and those who did not for negative affect which is to be expected. Gynaecologically immature women also had more negative affect. The reason for this is not clear, and such a relationship would require confirmation in a larger sample. There is other evidence in support of the idea that endogenous oestrogen levels achieved during pill cycles may be related to subjective state, or to trait variables like personality. In this sample women who retrospectively reported PMS were significantly more likely to have high N scores on the EPI. And they also tended to be the same women who had higher overall oestrogen levels with maximums above 30μg/gr., entering the early follicular phase range. Perhaps ovarian production of oestrogen has to exceed a certain level before it is detected by the brain, and alters the brain environment sufficiently to produce subjective state change, or more particularly heightened perception of physiological changes which are interpreted as PMS. On the other hand, endogenous oestrogen may simply reflect the underlying pattern of exogenous steroid metabolism which is primarily responsible for subjective outcomes. It is likely that N scores and retrospective PMS reporting are confounded which would explain why they are correlated. This does not explain the association of these traits with high E-3-G, however even *high* oestrogen levels were relatively conservative in comparison with the normal menstrual cycle.

The multivariate analysis which was performed on the data set was designed to test the effects of various specific oestrogen parameters on well being. Very few of these tests

were significant, but those that were suggest that there is a relationship between the absolute levels of endogenous oestrogen and well being, and that the relationship is stronger for physical changes than moods. At the end of the cycle when endogenous oestrogen was well suppressed bloating and breast tenderness were high, and when oestrogen recovered they declined. One possible explanations for this is that endogenous oestrogen suppression directly causes breast pain and distension. Alternatively the low oestrogen group may have had higher circulating or bioactive levels of exogenous (pill) steroids which were causing the breast tenderness, etc.. through more potent target tissue effects.

Because multiple statistical tests have been performed on a small data set, and the results are not highly significant, these findings must be interpreted as trends which require corroboration with a larger number of volunteers, preferably over a longer timespan. The important possibility that individuals have different patterns of mood and physical well being over the OC cycle because of different patterns of exogenous or endogenous steroids deserves further research attention in a sample of women who are experiencing marked cycle-related change.

Chapter 4 Assessment of Women's Menstrual Health Experience and Attitudes Towards Vaginal Bleeding

4.1 Introduction

In the previous chapter, the possible relationship between residual ovarian function and persistent variation in well being over the combined pill cycle was considered. This study showed that the amount of endogenous oestrogen released is not systematically related to fluctuations in well being (except possibly certain physical variables), nor could it explain fully the presence of these changes. There must be alternative explanations for the experience of cyclical change, and in particular the perception of about two-thirds of the women in the folliculogenesis sample that they had PMS. One very important possibility is that women's attitudes, and those of the society at large, about bleeding and related experience influence the way in which individuals process and report this experience. The idea which was considered in Chapter Two that vaginal bleeding and its sequelae are culturally symbolic is fundamental to our understanding of cycle-related changes in subjective well being.

It has been noted that attitudes to bleeding were relatively uninvestigated in Western industrialized societies before the 1980's (Brooks-Gunn & Ruble, 1980). One explanation for this is that a false dichotomy has been created in which women in Western societies are questioned about cycle-related symptoms and changes, while women in non-Western settings are questioned about their beliefs and practices pertaining to menstruation itself, i.e.- taboos (Paige-Ericksen, 1987). It is likely that symbolic experience is 'translated' in each culture, in a culturally appropriate way via the predominant thematic institutions of that society. Birke & Best (1982) suggest that in our society 'science' has replaced the 'mythology and religion' of so-called 'primitive' cultures as the generative source of menstrual negativism and tabooing.

Thus in our society where biological phenomena are dealt with almost entirely in terms of the medical model the prominent issue is cycle-related change, and in non-medicalized cultures behavioural proscriptions and ritual actions are the norm. At least this is the dichotomy which has been created. Yet there is evidence that "the beliefs about menstruating women in our own society share important similarities with the beliefs held in other cultures" (p.175, Paige-Ericksen, 1987), suggesting that we have more in

common with other cultures attitudinally than we are prepared to acknowledge. Equally women in non-urban, non-Westernized societies report experiencing psycho-physiological changes of a similar nature and magnitude to those reported in our society (Snowden &Christian, 1983). In this chapter semi-structured interviews and a questionnaire survey have been employed in a reflexive manner to obtain information about what women experience over their cycles and how they view this experience in order to broaden our understanding of women's menstruation-related beliefs and expectations.

4.2 Aims

The purpose of the research reported in this chapter is to broadly address if and why women attending an Edinburgh family planning clinic consider vaginal bleeding to be important. It is not possible in one chapter of this thesis to address all the complex questions surrounding the acquisition, expression, and meaning of attitudes and beliefs about menstruation. Thus, this chapter aims to describe some of these beliefs in relation to certain demographic characteristics of the Clinic population, such as contraceptive use. Finally this questionnaire survey provides a practical link with the rest of the thesis. Respondents were questionned about their willingness to undergo manipulations of their cycle length and the timing of bleeding, and at the same time given the opportunity to volunteer for the experimental investigation reported in Chapter Six which involves cycle length manipulation.

4.3 Methods of Assessment and Analysis

The findings in this chapter were derived from two different samples of women, all of whom were recruited from the main Family Planning Clinic (FPC) in Dean Terrace, Edinburgh. The first sample of twenty women who are described in the previous chapter, provided information through both a questionnaire (MHRAQ-1, see Chapter Three), and a semi-structured interview, and will be referred to as the folliculogenesis study volunteers. The second sample was comprised of approximately seven hundred consecutive FPC attenders, who completed a modified version of the MHRAQ-1.

4.3.1 The Semi-Structured Interview

The final meeting with the folliculogenesis study volunteers took the form of a semi-structured interview. This part of the study was seen as exploratory, and not hypothesis testing as such. It was intended to generate information in an open-ended way about women's beliefs. The interview schedule included questions about a number of topics related to a woman's reproductive attitudes and menstrual health experience: the pill, hormonal control, and contraception in general; pregnancy and childbirth experience; attitude, experience, and behaviour relating to menstruation; gender identity; personal relationships and sexuality. The qualitative interview method known as discourse analysis was used. The technique involves conducting a semi-structured or themed interview in which informants are encouraged to describe their own views and experience in their own language with limited leading and prompting by the interviewer (Lindzey & Elliot, 1985; Bogdan & Taylor, 1975; Lofland, 1971). A series of pre-set questions are covered during the course of the meeting, but not necessarily in a proscribed order.

The questions about menstruation[1] were derived from the common themes reported in the literature (eg.- Martin, 1989; Matlin, 1987; Birke & Best, 1982; Brooks-Gunn, 1985; Snowden & Christian, 1983), and covered menarchial experience, taboo, concealment, avoidances, positive aspects, equipment use, naming, cyclicity, and the desire to alter the cycle. The interview schedule was piloted with seven volunteers from the Centre for Reproductive Biology in Edinburgh, before it was used with the study sample. Questions that seemed to have little meaning or were too abstract were dropped or modified. Redundancies were omitted, and the order of questions was altered to be as logical and conversational as possible. The final schedule took approximately one hour to complete. The questions pertaining to vaginal bleeding experience are extracted below, while the complete interview schedule can be found in Appendix 4.01.

1
Since all of the women interviewed were taking the pill, they were not menstruating in the true sense. Where possible hormone withdrawal bleeds were discussed as 'bleeds', but occasionally 'menstruation' was used in a generic sense to mean vaginal bleeding. As will become apparent, most women do not make a distinction between menses and hormone withdrawal bleeds.

MENSTRUATION

Let's move on now to some questions about menstruation. In the questionnaire I asked you about your first period, and the way your family reacted to it- could you just tell me about that again.

Attitude, Experience, and Behaviour

Is menstruation something you feel able to speak openly about?
Who do you talk to about it? Other women? Your partner? Other men? Why or why not?
Do you think menstruation is still a taboo subject? Why?
Do you mind if people know you are bleeding? Why? Who?
If no- So why doesn't a woman who's at work or in the pub just walk to the toilet with a tampax in her hand.
So, what's the difference between having a cold and having a period? People tend to show off a cold and talk a lot about it, but women hide the fact that they have their period when ***all of us*** *bleed regularly?*
What do you think is positive about menstruation?
Do you think you are perhaps more aware of your surroundings, or more sensitive before or during your period?
Is there anything that you avoid doing while you are bleeding?
Do you have sex? If not- Why not? Who decides that? You, your partner, both of you?
Do you feel differently about yourself on the days that you are bleeding from the days when you are not?
What about at other times in the month? (Pre- post-menstrually)
Do other people notice the differences?
Do you think about menstruation when you are not bleeding?
What name do you use for menstruation?
Do you use pads or tampons?
Would you change your cycle if you could? (Either the pattern of bleeding or your physical and emotional experiences of it.) Why or why not? In what way?

The interviews with the study sample were audio-taped for later transcription. Four of the 20 interviews were recorded using an old model Sony tape recorder, but the sound quality on these tapes was poor, and a Sony Professional Walkman was purchased to carry out the remaining interviews. One of the twenty tapes was too indistinct to transcribe verbatim (M3). General points could be discerned from this tape, but quotes are not taken from it for the analysis. Full transcriptions were made of the other 19 tapes, and these were used in the analysis.

The interview transcripts provided a rich source of information on women's attitudes to vaginal bleeding and other aspects of reproductive health. It is beyond the scope of this thesis, however, to fully explore these findings here. Nevertheless, the interview transcripts were used as source material in the development of the Menstrual Health and Reproductive Attitudes questionnaire- version two.

4.3.2 Menstrual Health and Reproductive Attitudes Questionnaires

There is no single questionnaire in the published literature which comprehensively gathers information about bleeding experience, contraceptive use, experience of cyclical change, attitudes and practices relating to bleeding and contraceptive use, willingness to alter the cycle, and demographic variables which may be related to all of these factors. Several questionnaires and research projects have separately addressed these different aspects including the Menstrual Attitudes Questionnaire (Brooks-Gunn & Ruble, 1980) and the Menstrual Elimination Questionnaire (Miller & Smith, 1975) amongst others (Jarvis & McCabe, 1991; [Ruder & Finn, 1981 in] Paige-Ericksen, 1987; Brooks-Gunn, 1985; Snowden & Christian, 1983; Spencer-Gardner, et al.,1983; Paige, 1973; Berry & McGuire, 1972; Moos, 1968). Aspects of many of these have been incorporated into the Menstrual Health and Reproductive Attitudes questionnaire used in this chapter (MHRAQ-2).

The development of version one of the MHRAQ was described in Chapter Three. MHRAQ-2 had three purposes: 1) it offered a means to gather demographic information about the clinic population; 2) it provided a tool to test the generalizability of the menstrual attitudes derived from MHRAQ-1 and the semi-structured interviews; and 3) it functioned as a recruitment device for the pill cycle length manipulation study which is reported in Chapter Six.

MHRAQ-2 was based on MHRAQ-1, but was modified to accommodate the broad scope of ideas generated by the semi-structured interviews. The order and wording of questions was changed, and in some cases simplified, to make it possible for women to complete the questionnaire without assistance while waiting in the FPC for a consultation. A copy of MHRAQ-2 is contained in the Appendix 4.02. A special "supplement" was added to the basic questionnaire comprised of quoted statements made by women in the open interviews, or précis of views held by more than one woman. The supplement consisted of a list of 37 statements with which respondents could agree or disagree.

The supplement included statements relating to the nature of bleeding, embarrassment linked with bleeding, neutral, positive, and negative views, awareness of other women's bleeds, perceptions of men's views, and thoughts about menstrual education and the use of menstrual equipment. It was intended that the supplement should cover

a wide range of ideas and possess a balanced tone with some statements phrased positively and some negatively, some with a feminist slant and some without. The objective was to force women to consider each question in turn, and not produce a response set.

The questionnaire was piloted with 20 Clinic attenders. Each woman was asked to complete the questionnaire without assistance. I then went through it with her item by item to determine what she understood each question to mean and how she thought it could be improved. The questionnaire was refined in consideration of these discussions, however, it was not formally validated.

In December 1989 and January 1990 the MHRAQ-2 was offered to every woman who attended the FPC over the course of fourteen Clinic days, covering a total of thirty-eight Clinic sessions. Attenders at the FPC are made up predominantly of women coming for routine family planning consultations. A much smaller proportion attend for colposcopy treatment, well woman services, or accompany partners to vasectomy counselling and surgery. Women also attend for Menopause Clinics on Wednesday afternoons, but they were not asked to take part. The numbers of women passing through the clinic during these three weeks are summarized below.

Weekly subtotals of FPC attendance-Week:	11th to 15th Dec., 1989	437
	8th to 12th Jan., 1990	560
	15th to 18th Jan., 1990	493
Total numbers attending FPC	11th Dec. to 18th Jan.	1490

One thousand and eighteen (1018) questionnaires were handed out to consecutive clinic attenders and 698 were satisfactorily completed and returned. Of those completed, a random sample of five hundred (500) were coded and the data were entered into the University of Edinburgh main frame computer. The data were verified using fortran programmes written by Dilys Rennie and analysed using SPSS-x.

The analysis which is reported below addresses the following questions: 1) What are the demographic characteristics of Clinic attenders? 2) Does this population consider vaginal bleeding important and why? 3) Were the women who took part in the folliculogenesis study demographically and attitudinally representative of this larger cross-section of Clinic attenders? 4) Do women using the pill experience or perceive

their vaginal bleeding or other cycle related experiences differently to women not using the pill? And 5) Are those women who volunteered to take part in the cycle length manipulation study different from those women who did not volunteer? An assessment was made of the frequencies of responses of the whole sample to each question. Comparisons of the response frequencies of pill versus non-pill users, and volunteers versus non-volunteers were made using Chi-square (χ^2) tests, with Yates correction for small cell size where appropriate.

4.4 Characteristics of the Family Planning Clinic Population

4.4.1 Demographic and Contraceptive Features

Estimations of the frequency distributions of demographic characteristics of the random sample of 500 hundred FPC attenders shows them to be largely homogeneous. Clinic attenders tend to be highly educated, non-religious, working women who are in relationships with equally non-religious, largely professional, working men. As one might expect, the age distribution of the sample, shown in Table 4.01, covers the entire reproductive span, with almost three-quarters aged between 20 and 34 years. Approximately two-thirds of respondents possess degrees or post-graduate qualifications, and more than 70% are in full time employment. Most women also work in professional, managerial, or support and trained traditional white collar jobs including: doctors, lawyers, corporate executives, nurses, teachers, social workers, lab technicians, bookkeepers, personal assistants, etc.. Further almost 40% of partners are professionals or managers. Therefore, the vast majority of respondents may be classified as belonging to social classes I and II and to a smaller extent, III according to the indices provided by OPCS (1980) (see Table 4.01).

More than 90% of women report that they are presumptively fertile, and 86% (of the 90% who replied to the question) are in a sexual relationship. Only about 30% of the sample have ever been pregnant, and 9% of first pregnancies were terminated. Of women reporting that they have a religion, 60% are Protestant and 12% Catholic. The remainder report no religion or did not reply to the question. Less than a third consider themselves to be religious people, and only 14% say that they are currently active in their religion. The distribution of partner's religions is similar, and even fewer partners are reported to be religiously active (see Figures 4.01 and 4.02).

Table 4.01 Biographical Details of Questionnaire Respondents: Comparisons by pill use and volunteering

Variable	Classification	n=	%	χ^2 for pill vs. non pill users	χ^2 for volunteers vs. non volunteers
Age	-19	31	6.2	18.28**	8.86
	20-24	132	26.4		
	25-29	148	29.6		
	30-34	88	17.6		
	35-39	59	11.8		
	40+	34	6.8		
	Missing data	8	1.6		
Relationship status	In a relationship	429	85.8	0.00	0.00
	Not in a relationship	25	5.0		
	Missing data	46	9.2		
Highest educational attainment	School leaver	90	18.0	3.85	3.96
	Highers	90	18.0		
	University/Poly./College	239	47.8		
	Postgraduate/Profession	75	15.0		
	Missing data	6	1.2		
Employment status	Full time job	353	70.6	27.43**	8.33
	Part time job	43	8.6		
	No paid job	39	7.8		
	Student	54	10.8		
	Missing data	11	2.2		
Respondents' social group	Prof./Manag./Self-empl.	95	19.0	15.87*	10.56
	Support/Trained Traditnl	258	51.8		
	Service/Manual	46	9.2		
	Home/Student/Unempl.	89	17.8		
	Missing data	12	2.4		
Partners' social group	Prof./Manag./Self-empl.	194	38.8	Not tested	Not tested
	Support/Trained Traditnl	128	25.6		
	Service/Manual	83	16.6		
	Student/Unemployed	44	8.8		
	Missing data	51	10.2		

Table 4.01 Continued

Variable	Classification	n=	%	χ^2 for pill vs. non pill users	χ^2 for volunteers vs. non volunteers
Fertility status	Presumptively fertile	462	92.4	Not tested	Not tested
	Sterilized	7	1.4		
	Partner sterilized	4	0.8		
	Menopausal	1	0.2		
	No sexual realtionship	18	3.6		
	Trying to conceive	8	1.6		
Parity	Nulliparous	321	64.2	69.87**	4.21
	1 pregnancy	64	12.8		
	2 pregnancies	47	9.4		
	3 pregnancies	25	5.0		
	≥4 pregnancies	12	2.4		
	Missing data	31	6.2		

Key: *p<0.05, **p<0.00, volunteers- those women who agreed in principle to take part in the cycle manipulation study reported in Chapter Six.

More than two-thirds of these women are currently using the pill as their method of contraception, and the majority have used their current method for more than one year. The other commonly used methods include the intrauterine contraceptive device (IUCD), female barrier methods, and condoms. More than half of the sample has also used the pill at some time in the past, and 36% report condom, 12% female barrier method, and 7% IUCD use in the past (see Figures 4.03 and 4.05).

Of current pill takers approximately 70% have used the pill for at least one year. Figure 4.06 shows that about 40% of those who could specify which type of pill they use are taking monophasic combined pills, while only about 12% of women use triphasic combined pills, and about 10% use progesterone only contraception. Thus pill takers at the FPC are predominantly established users of low dose pills. The distribution of ages at first pill use are shown in Figure 4.07. Two-thirds of women started the pill between the ages of 16 and 20, and only 9% of the 500 have never used this method.

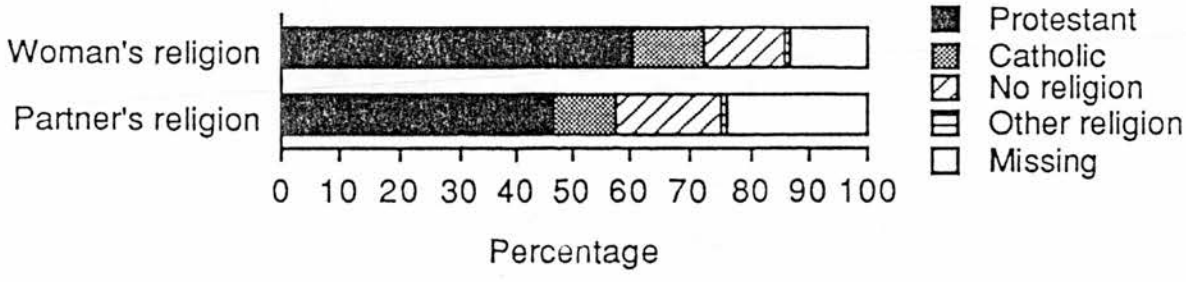

Figure 4.01 Religious affiliations of respondents and their partners.

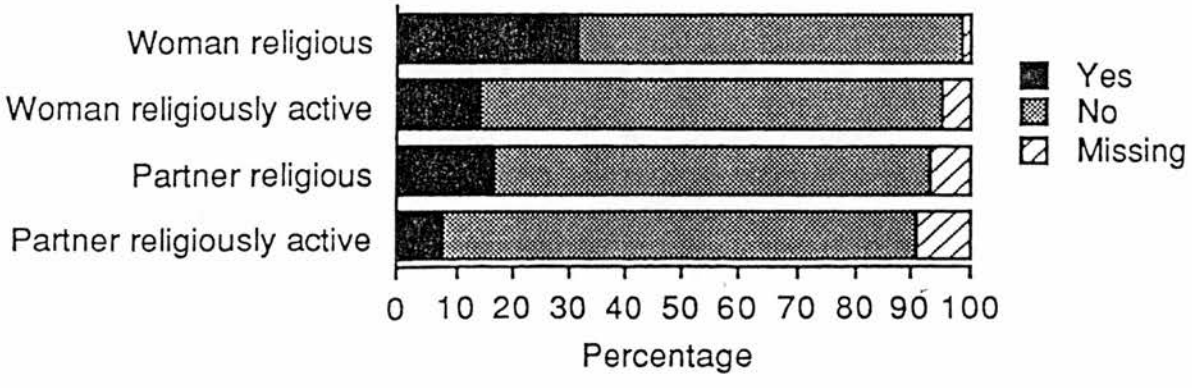

Figure 4.02 Strength of religious beliefs and participation in religious activities of respondents and their partners.

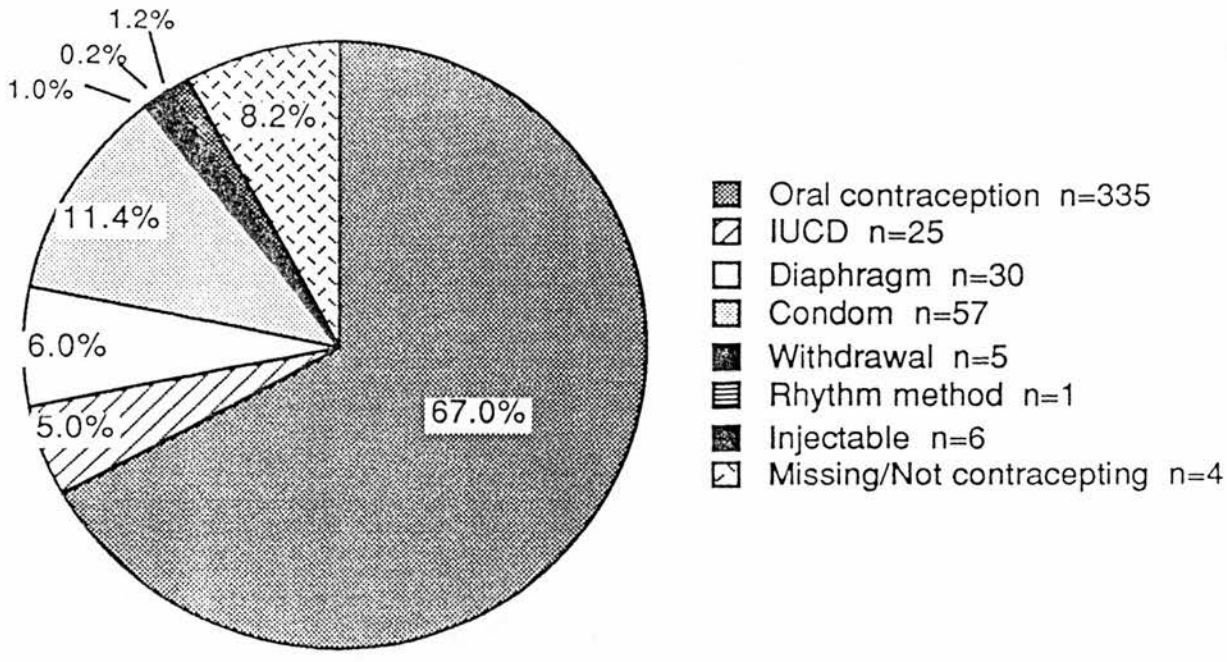

Figure 4.03 Present contraceptive method.

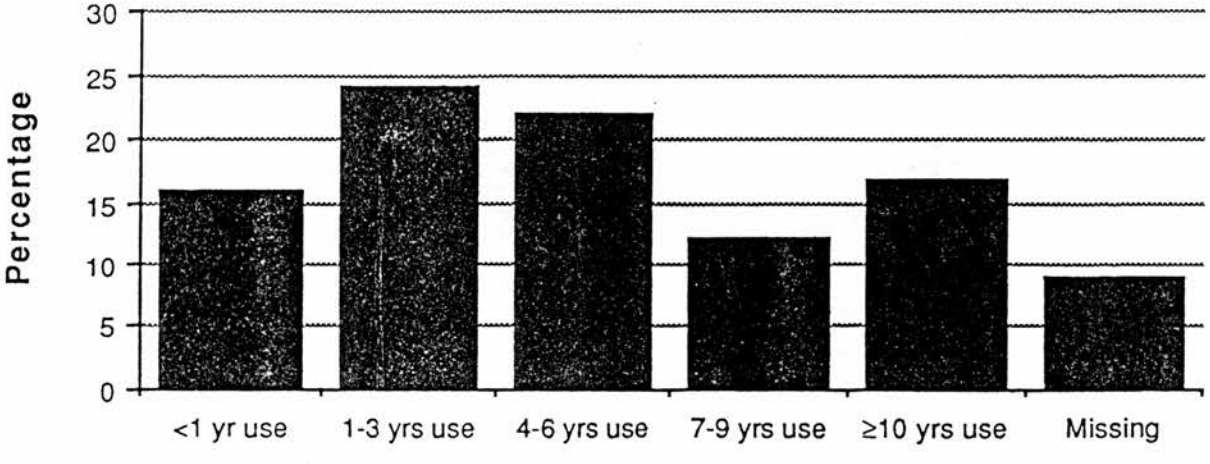

Figure 4.04 Duration of present contraceptive method use.

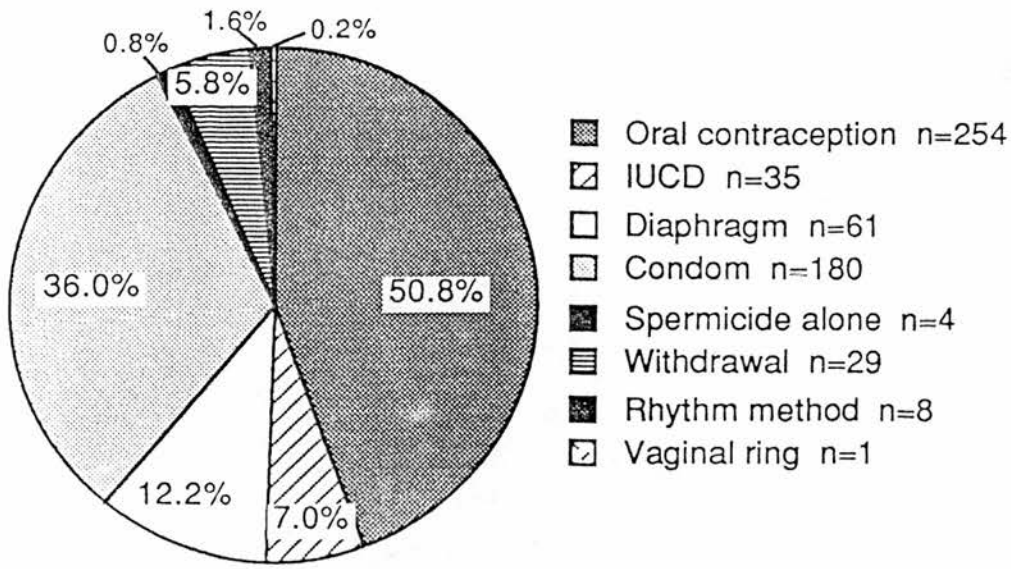

Figure 4.05 Previous contraceptive method usage. Totals greater than 100% due to past use of more than one method.

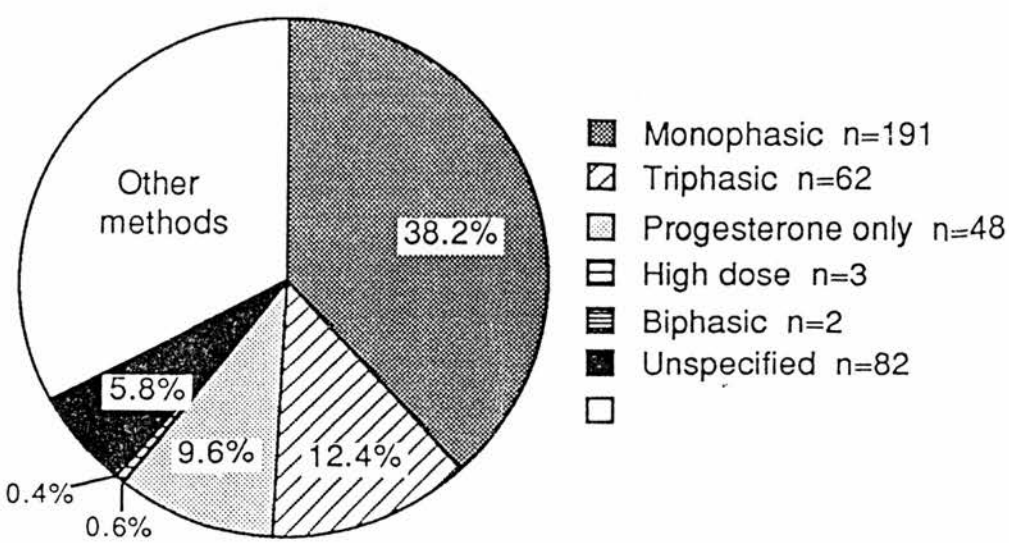

Figure 4.06 Current use of different pill formulations.

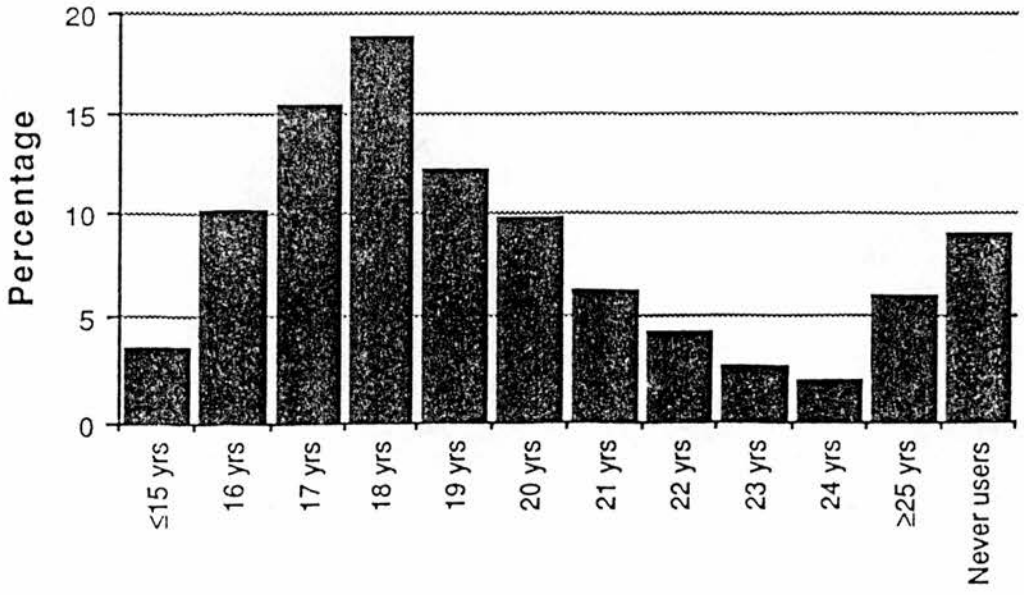

Figure 4.07 Age at first pill use.

4.4.2 Current Bleeding Experience

Approximately one-fifth of respondents report that they have light bleeds, three-fifths moderate, and one-fifth heavy to very heavy. The duration of the bleed was similarly distributed between 2 to 3, 4 to 5, and 6 to 7 days. Further about two-fifths each of the sample noted that full bleeding lasts for 1 to 2, or 3 to 4 days (see Table 4.02). Table 4.02 shows the incidence of breakthrough bleeding, and the variability of cycle length. The majority of women surveyed use only tampons to collect their menstrual blood. This is split about evenly between tampons with applicators and those without. The other third of women use pads some or all of the time, with or without tampons.

Table 4.02 Details of Bleeding for Questionnaire Respondents: Comparisons by pill use and volunteering

Variable	Classification	n=	%	χ^2 for pill vs. non pill users	χ^2 for volunteers vs. non volunteers
Reported volume of blood loss	Light	103	20.6	33.67**	2.04
	Moderate	288	57.6		
	Heavy	78	15.6		
	Very heavy	22	4.4		
	Missing data	9	1.8		
Duration of bleeding	2-3 days	64	12.8	Not tested	Not tested
	4-5 days	303	60.6		
	6-7 days	103	20.6		
	8-9 days	5	1.0		
	>10 days	8	1.6		
	Missing data	17	3.4		
Number of days of full bleeding	1-2 days	229	45.8	Not tested	Not tested
	3-4 days	205	41.0		
	5-6 days	27	5.4		
	7-8 days	2	0.4		
	Missing data	37	7.4		

Table 4.02 Continued

Variable	Classification	n=	%	χ^2 for pill vs. non pill users	χ^2 for volunteers vs. non volunteers
Variability in cycle length	Always the same	218	43.6	Not tested	Not tested
	2-3 days variation	170	34.0		
	5-6 days varaition	53	10.6		
	>10 days varaition	34	6.8		
	Missing data	25	5.0		
Incidence of breakthrough bleeding	Never	266	53.2	Not tested	Not tested
	Some cycles	128	25.6		
	All cycles	18	3.6		
	In the past	75	15.0		
	Missing data	13	2.6		
Menstrual equipment used	Tampons w/ applicator	183	36.6	9.23*	5.41
	Tampons w/out applictr.	152	30.4		
	Pads only	56	11.2		
	Pads with tampons	53	10.6		
	Pads or tampons	47	9.4		
	Missing data	9	1.8		
Reported PMS status	Yes PMS	147	29.4	5.09	8.36*
	Maybe PMS	126	25.2		
	No PMS	161	32.2		
	Past PMS	42	8.4		
	Missing	24	4.8		

Key: *p<0.05, **p<0.00, volunteers- those women who agreed in principle to take part in the cycle manipulation study reported in Chapter Six.

4.4.3 Cycle-Related Changes in Well Being

Approximately 55% of women surveyed said that they did have, or might have PMS. About one-third said that they did not have it, and 8% felt they had had it sometime in the past (see Table 4.02). Respondents were presented with a large number of aspects of well being which might change with a regular pattern over their cycle. Figure 4.08 shows the percentages of women who indicated that they experience a particular sensation/feeling cyclically. Bloating (60%), breast tenderness (58%), and period type

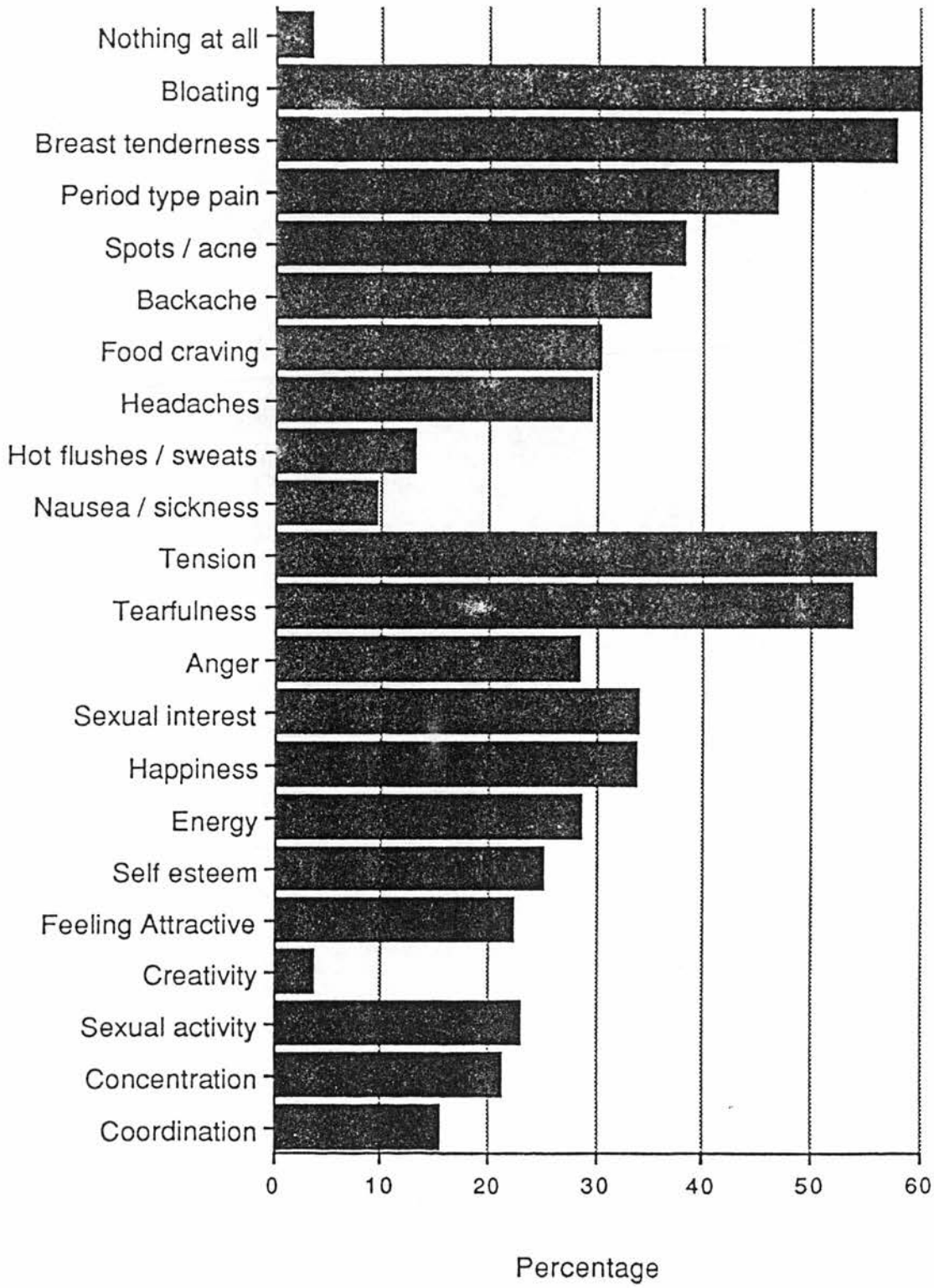

Figure 4.08 Incidence of self-reported cycle-related "symptoms".

pain (47%) are the most commonly reported physical symptoms. Tension (56%) and tearfulness (54%) are the moods which were most frequently reported to cycle[2]. Generally positive moods and cognitive/behavioural variables (lower 9 bars on figure) were reported by fewer women to vary cyclically than negative moods and physical states (upper 12 bars).

4.5 Attitudes and Behaviours of the FPC Population in Relation to Bleeding

Almost three-quarters of the 500 respondents believe that it is important for women to have periods (see Figure 4.09). The reasons which women gave on MHRAQ-1 and in the interviews for finding bleeding important were incorporated into question 29 on MHRAQ-2. Figure 4.10 summarizes respondents' characterization of the importance of bleeding. Namely, the majority agreed that bleeding is natural, a good indication of non-pregnancy, normal, shows that one is using contraception properly, a sign of good health, a nuisance, a sign of fertility, and a habit. On the other hand, they disagreed that it was unnecessary when using reliable contraception, a waste of bodily energy and nutrients, emotionally cleansing, womanly, and physically cleansing. These later statements also seemed to hold more limited meaning for women which is indicated by the fact that 34% or more of women answered that it was not a belief they hold. However, the fact that only 2 to 7% of women failed to respond to any part of this question indicated that it was generally easily intelligible and meaningful.

Those activities which women avoid during vaginal bleeding are summarized in Figure 4.11. The only things avoided to a significant degree seem to be sexual intercourse, and swimming. Over half of respondents observe the "sex taboo". More complex aspects of women's beliefs about and attitudes to bleeding were explored using the 37-statement "supplement" described above. Like the other Likert-type scales used in this questionnaire the 'meaningfulness' of the statement was revealed by how polarized responses were into agree/disagree categories versus 'neither agree nor disagree' or missing entries. All responses are summarized in Appendix 4.03.

2
Irritability and depression, which are possibly the most commonly reported PMS-type 'symptoms' (eg.- Warner, et al., 1991) were unfortunately overlooked in this list. Depression could be indicated by cyclical 'happiness', and 'anger' might be interpreted by some as analogous to irritable. However, the relatively limited reporting of 'happiness' and 'anger' suggest that 'irritability' and 'depression' ought to have been specified.

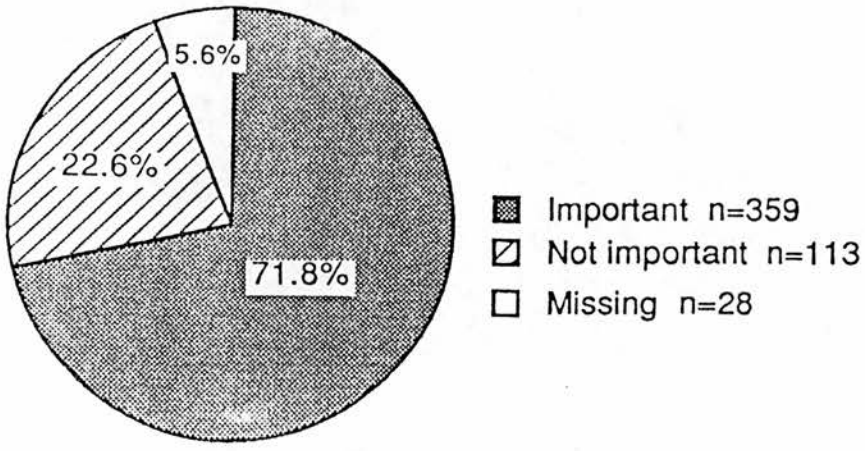

Figure 4.09 Respondents beliefs about whether or not it is important for women to have periods.

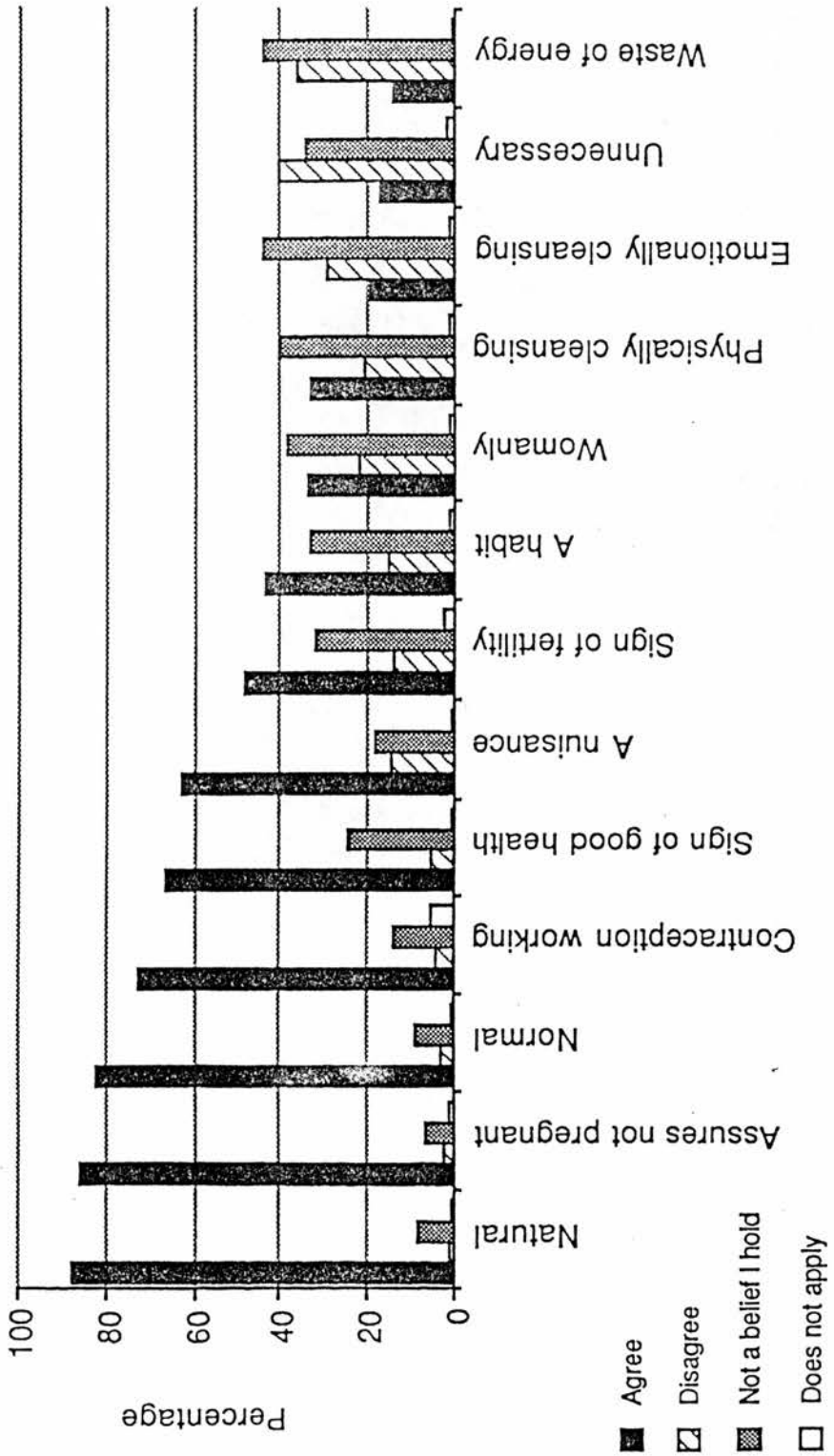

Figure 4.10 Specific beliefs about menstrual bleeding.

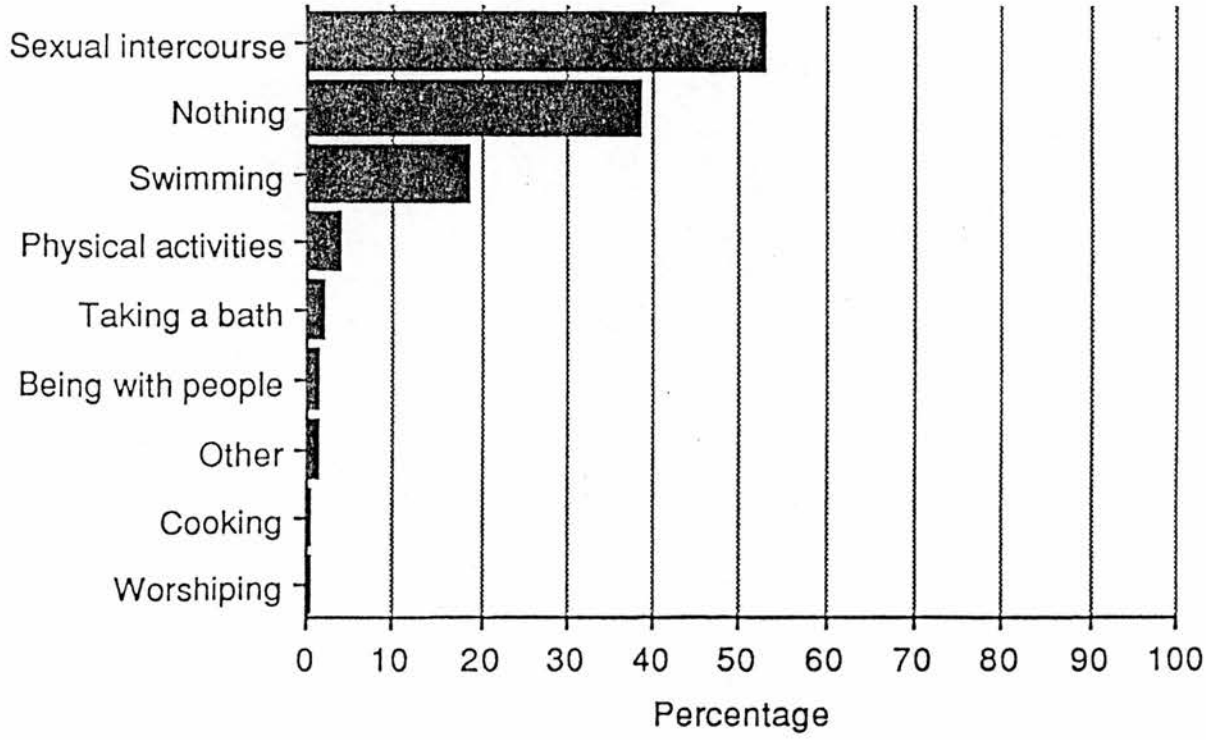

Figure 4.11 Incidence of menstrual taboo observance.

Statements which related to the instruction which should be given to children regarding menstruation, the provision of equipment, bleeds as something embarrassing, and bleeds as a neutral experience produced the most definitive responses. From 63 to 86% of women agreed or strongly agreed that both boys and girls should be taught at school and home about periods, and that girls should be shown how to use menstrual equipment. About 50% of respondents believe that most people are embarrassed to talk about periods, however, an equal proportion do not believe that tampons are embarrassing to others. Because of the way in which the statement was phrased, their replies do not preclude the possibility that they do hide menstrual equipment because they themselves find its use embarrassing. More than three-quarters of women agreed that although they are less embarrassed by bleeding than they were when they were younger, they would be embarrassed if they bled onto their clothing.

A marked majority of women agreed that bleeding does not affect them a great deal, and is not positive or negative, but "just there". While 38% disagreed that for them menstruating is just another toilet habit, 32% agreed that it is. In contrast to the response to neutral statements the majority of women disagreed with specifically positive *and* negative statements about bleeding. Overall women do not find that bleeding makes them feel relaxed, proud of being a woman, or is mainly a positive experience. On the other hand, they also do not believe that bleeding "gets rid of their rottenness", is a curse when it is painful, or makes them feel dirty. Women also tended to disagree that the men they are in contact with view bleeding negatively, as painful and traumatic, do not want to discuss it, or use it to stigmatize women. In contrast, about three-quarters agreed that their own partners are sensitive and understanding when a bleed affects them badly.

The reasons that more than half of women avoid sexual intercourse during bleeding seem to be complex from their response to statements relating to menstrual sexuality. Most women do not think tampon use is interpreted as being sexual, nor do they think that it is morally wrong to have sex during a bleed. Equally, they do not avoid sex for fear of getting blood on their partner. However, most do not feel especially sexually receptive during a bleed and agree that they prefer not to have sex then because it is messy.

The statements which seemed to possess the least meaning for women were those relating to the nature of menstrual bleeding, and women's awareness of and solidarity

with other women who are menstruating. These produced 'neither agree nor disagree' responses between 22 and 48% of the time. About a third to one half of women agreed that periods are to do with sex and babies, that they are private and personal, and that the more a woman bleeds the more she is affected by it. More than half of respondents are unaware that other women are bleeding, and while a quarter of women believe that they notice menstrual blood's distinct smell, more than a third do not. The majority of women could not relate to statements which indicated that bleeding made them feel closer to other women, to their own mortality, or physically unique.

In spite of the importance with which most women view bleeding 52% have altered their pill cycle length in the past (see Figure 4.12). The question relating to why the cycle was altered and in what manner was not answered by the majority of women. Nevertheless, of those responses given the most common practice seems to have been to take 2 packets of pills in a row (20%) in order to avoid a bleed while on holiday (23%). When women were asked if they would eliminate bleeding for a time if there were no harmful consequences and they could be sure that they were not pregnant almost four out of five said they would possibly or very likely do so (see Figure 4.13). Less than one third of respondents said they were not likely to, or would definitely not do so.

4.6 Representativeness of the Folliculogenesis Sample

The folliculogenesis study sample of Clinic attenders was highly representative of FPC attenders at large. They were selected for established pill use, so are in this way similar to two-thirds of Clinic attenders. Their educational attainments and employment status, religion, relationship status, and parity are all similar to the general FPC sample. The distribution of volume and duration of vaginal bleeding reported by the 500 FPC attenders is also very similar in this sample.

Equally the beliefs of the larger sample about the importance of bleeding are similar to those of the small sample of pill takers from which the questions are derived. Thus, vaginal bleeding was seen as a sign of health, naturalness, and potential fertility, in spite of the fact that bleeding on the pill is an artificial consequence of hormone withdrawal and ovulation is not taking place. Several folliculogenesis volunteers said

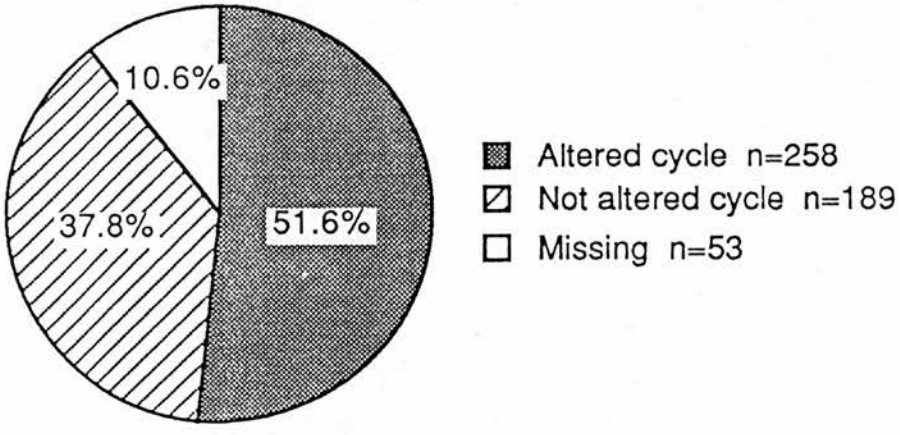

Figure 4.12 Incidence of previous pill cycle length alteration.

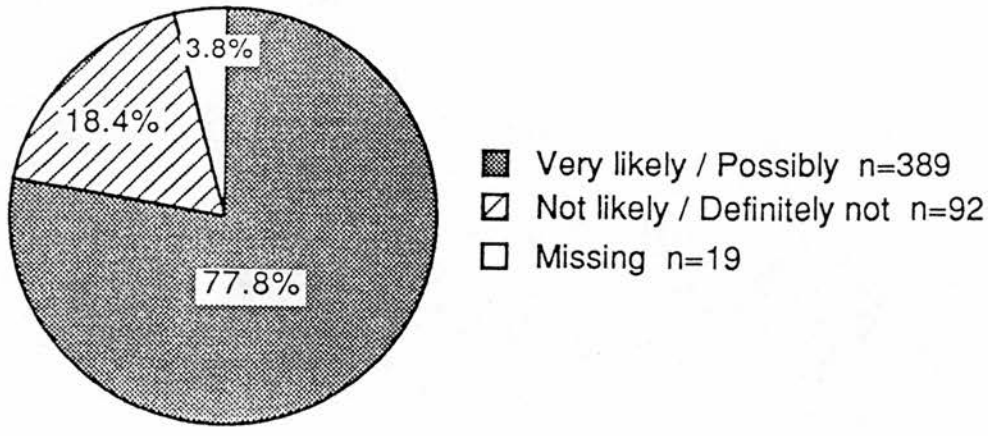

Figure 4.13 Hypothetical willingness to eliminate vaginal bleeding for a time.

that regular bleeding was a sign that their bodies were "working normally". Another women said it was important to bleed because you are "supposed to"; another that it gives a "feeling of routine". Others said women bleed to "clear the womb" or for "cleansing once a month". And although withdrawal bleeding may still occur in the pill cycle if a woman is pregnant, these women felt that their bleeds reassured them that the pill was working properly, that they were using it correctly, and that they were not pregnant.

Three women did not believe that bleeding on the pill was important. One, who is a botanist, said that it is a "waste of energy" to bleed, and another who is a biochemist, said it was not important if you were taking the pill, but was an important sign of non-pregnancy during a "normal cycle".

Ten of these volunteers had altered the length of their pill cycle at some time in the past. In eight cases the number of active tablets taken was extended beyond the usual twenty-one. Most often a woman simply took two packets of pills in a row, usually because she wanted to avoid a period on holiday. One woman takes several packets in a row routinely (the "tricycle regime"). Two women shortened the number of active pills to advance bleeding. One wanted a 'period' before she went on holiday, and one stopped her pills early when she had breakthrough bleeding brought about by vomiting.

Women were asked how they would feel about eliminating withdrawal bleeding for a time if there were no harmful physical consequences. Curiously, although ten women had altered bleeding in the past, only eight said they would be very likely to do so in future. Of the women who had previously taken extra pills to avoid bleeding while on holiday, one said she would "definitely not" alter her cycle, and another said she was "not likely" to do so, yet neither had had any problems with the manipulation. In spite of these apparent contradictions, the majority of women expressed a willingness to alter the cycle. The four possible responses were selected in precisely the same proportions as the general FPC sample: "very likely" 8, "possibly" 8, "not likely" 3, and "definitely not" 1.

The proportions of women retrospectively reporting PMS were similar in the study sample to the larger sample. The prospective findings of the investigation seem to support the reports made by the larger sample that bloating, breast tenderness, and period type pain are the most frequently experienced cycle-related changes.

4.7 Differences Between Pill and Non-pill Users

The fact that a sample of 20 separately recruited pill takers were so similar in demographic, experiential, and attitudinal variables to a random sample of 500 Clinic attenders who were using the full range of contraceptives begins to suggest that pill and non-pill takers attending the FPC are not materially different. A direct comparison between those taking the pill and all those using other methods of contraception within the MHRAQ-2 sample shows that the two groups are generally quite similar. They differ in the ways that are to be expected given the contraception which they are using.

The first way in which the groups differ is by age. The Chi-square test showed that pill takers were significantly younger than non-pill takers ($p<0.00$; see Table 4.01 for χ^2 statistics). Eighty per cent of pill takers are between 20 and 34, while a quarter of other method users are 35 or older, the time after which pill use is discouraged, especially in smokers. Non-pill takers were also significantly less likely to be in full time employment (79% pill vs. non-pill 58%) and more likely to be unemployed (7% pill vs. non-pill 11%), in part time work (5% pill vs. non-pill 17%), or a student (10% pill vs. non-pill 14%; $p<0.00$). In parallel to this, significantly fewer non-pill women were in the professional/managerial bracket (22% pill vs. non-pill 15%), while significantly more classed themselves as homeworker/ student/ unemployed, (15% pill vs. non-pill 27%; $p<0.05$). Some of these differences may be attributable to the fact that the non-pill group had significantly higher parity ($p<0.00$). While 80% of pill takers had never had a pregnancy only 44% of non-pill takers were nulliparous. Nineteen per cent of pill takers have had between one and four pregnancies, versus 56% of non-pill takers. The two groups did not differ in their relationship status or their level of education, however (see Table 3.01).

As one would expect, pill and non-pill users differed on almost all aspects of their attitude to current contraceptive use in ways which seem to relate directly to the effects of the various methods. The amount of blood loss which women reported was also strongly related to method use. While similar proportions of both groups report moderate bleeding (59% pill vs. 58% non-pill), many more pill users indicate light bleeding (27% pill vs. 8% non-pill), and many more non-pill users heavy to very heavy bleeding (14% pill vs. 34% non-pill; $p<0.00$). Pill users are significantly more likely

to use tampons (72% pill vs. 58% non-pill), than pads with or without tampons (28% pill vs. 42% non-pill; $p<0.05$). See Table 4.02 for χ^2 statistics.

In spite of the fact that non-pill users tend to bleed more heavily than pill users, the two groups do not differ in the degree to which they consider bleeding important ($\chi^2=0.00$, $p=0.98$), nor in the reasons they cite for its importance. The groups did not differ in their willingness to eliminate bleeding if they could ($\chi^2=1.36$, $p=0.71$). However, significantly more pill takers have altered their cycle length in the past (48% pill vs. non-pill 30%; $\chi^2=8.99$, $p<0.01$).

There were significant differences between the groups on only 4 of the 37 statements on the questionnaire supplement. These differences suggest slight and subtle differences in the attitudes to their bleeds of women using different contraceptive methods. The views of the non-pill group, who have higher parity, were significantly more polarized on the statement suggesting that periods are experienced differently after having children ($\chi^2=24.73$, $p<0.001$). Their views on the nature of bleeding were different to pill takers. In particular, they were more inclined to disagree that bleeding is private and personal (% disagreeing- 13% pill vs. 24% non-pill; $\chi^2=18.57$, $p<0.001$), and agree that it brings women closer to their "physicalness" (% agreeing- 22% pill vs. 38% non-pill; $\chi^2=17.13$, $p<0.01$). Finally, non-pill takers are significantly less likely to find their partner sensitive and understanding when their period affects them badly (% disagreeing- 3% pill vs. 14% non-pill, $\chi^2=17.86$, $p<0.01$).

Women who do and do not use the pill did not differ significantly in the frequencies with which they report suffering from PMS (see Table 4.02). However, they do differ in the incidence of some self-reported cyclical symptoms. Namely, non-pill takers report a higher incidence of cyclical change in tension ($\chi^2=8.19$, $p<0.01$), breast tenderness ($\chi^2=5.35$, $p<0.05$), and backache ($\chi^2=6.29$, $p<0.05$). There is also a non-significant tendency for them to report more cyclical period type pain ($\chi^2=3.02$, $p=0.08$), anger ($\chi^2=3.18$, $p=0.07$), energy ($\chi^2=2.40$, $p=0.12$), and creativity ($\chi^2=2.57$, $p=0.10$). On the other hand, there are no group differences in the incidence of cyclical happiness, self-esteem, attractiveness, coordination, concentration, bloating, hot flushes, or food craving. Nor are there any difference in variables which may be altered by pill use, namely: tearfulness (depression), headaches, nausea, sexual interest and activity, and acne.

Pill takers and other method users were not compared on measures of partner's status, religion, duration of method use, menarcheal experience, bleed duration, cycle length, breakthrough bleeding, or menstrual avoidances.

4.8 Differences Between Manipulation Study Volunteers and Non-Volunteers

All women taking the pill were asked if they would like to volunteer to take part in a further study relating pill cycle length to well being. This was the primary, but not the only device used to recruit participants into the study described in Chapter Six. It is of interest to explore whether or not there are any systematic biographical or attitudinal differences between pill takers who did and did not volunteer to take part in a study of cycle length manipulation. The comparisons reported here do not describe the differences between the actual participants and non-participants. Many women expressed a willingness to take part in the investigation but ultimately declined to join the study for a variety of reasons. The statistical comparisons are made between women who agreed *in principle* to the idea of taking part versus those who were unwilling even to be contacted. One hundred and seven or 32% of pill takers in the random sample of 500 offered their name and address to be contacted about the further study. The remaining 228 pill takers (68%) did not give any contact information. Thus these comparisons are made amongst the 335 "volunteers" and "non-volunteers" in the sample who were taking the pill. The same variables were compared as for the pill/non-pill groups above.

Overall there were relatively few differences between the groups. Notably, there were no differences in demographic variables, but there were slight differences in attitudes. Volunteering women indicated that they were "encouraged" to use the pill because it is separate from intercourse (89% volunteers vs. 76% non-volunteers; $\chi^2=7.79$, $p<0.05$), and because it caused an improvement in their PMS (47% volunteers vs. 29% non-volunteers; $\chi^2=11.04$, $p<0.05$), while non-volunteering women were "put off" by the effects which the pill has on their hormones and their system (42% volunteers vs. 37% non-volunteers; $\chi^2=8.37$ $p<0.05$). The views of women who volunteered were significantly more polarized into agree and disagree catergories over the idea that bleeding is a habit than the non-volunteers. Equally volunteers were significantly more likely to disagree that their periods are not positive or negative, "just there" (20%

volunteers vs. 12% non-volunteers; χ^2=9.95, p<0.05), and "just another toilet habit" (49% volunteers vs. 35% non-volunteers; χ^2=9.24, p<0.05). Volunteers agreed more strongly than non-volunteers that instruction about periods (40% volunteers strongly agree vs. 26% non-volunteers; χ^2=9.02, p<0.05) and equipment (68% volunteers strongly agree vs. 66% non-volunteers; χ^2=10.08, p<0.05) should be more freely available. They also tended to agree that pain is "the curse" (42% volunteers vs. 29% non-volunteers; χ^2=9.59, p<0.05), and that the more one bleeds the more one is affected by it (64% volunteers vs. 52% non-volunteers; χ^2=9.94, p<0.05).

The only other ways in which the two groups differed according to Chi-square tests were in the distribution of their PMS reporting, and one cyclical symptom. Those volunteering were more likely to report that they do *have* PMS, or have *had in the past*, and less likely to say that they *might* or do *not have* it (Yes PMS 33% volunteers vs. 26% non-volunteers, No PMS 30% volunteers vs. 36% non-volunteers, Maybe PMS 22% volunteers vs. 30% non-volunteers, Past PMS 15% volunteers vs. 7% non-volunteers; χ^2=8.36, p<0.05). They were also more likely to report cyclical food craving (37% volunteers vs. 27% non-volunteers; χ^2=3.55, p<0.05). The two groups did not differ in their willingness to eliminate bleeding if possible, however, there was a slight tendency for more volunteers to say that they would be likely to do so (85% volunteers vs 80% non-volunteers; χ^2=7.13, p=0.06).

4.9 Discussion of Findings

The aims of this chapter were to describe the characteristics of the samples studied in this thesis, to assess the importance of bleeding experience to them, and to consider the cultural filtering of attitudes and beliefs which may influence the reporting of cycle-related experience.

4.9.1 Demographic Factors and Menstrual Health in the Whole Sample

The sampling for the studies reported in this thesis is population based, and thus has an advantage over many other studies of attitudes and cycle-related change which have used students or nurses as a sample pool (Dan, et al., 1980). However, the results of MHRAQ-2 indicate that Edinburgh Family Planning Clinic attenders are not representative of the whole range of Scottish women of reproductive age. There is a strong bias in favour of higher social class, working women in their 20's who are

nulliparous and take the pill. Given that the experimental studies in this thesis are entirely concerned with established pill takers, however, this would seem to be an appropriate recruitment centre. The volume and duration of bleeding reported by women in this sample is similar to other samples, eg. moderate bleeds lasting for four to five days, and consistent with the high incidence of pill use.

Choice of menstrual equipment has been related to the degree of traditionalism in menstrual attitudes, with tampon use being associated with more liberal beliefs. Snowden & Christian (1983) note that tampons tend to be used by urban, middle class women, and in support of this most of this sample use tampons. Paige (1973) interprets the rejection of tampons as "an indirect measure of anxiety about the invasion of one's body, and about the sexual overtones of menstruation". This precept is partly borne out by the fact that FPC attenders not using the pill were somewhat more likely than pill takers to use pads. This may either be a function of apparently, slightly more conservative attitudes to their bodies and bleeding (see below) or due to the fact that their bleeds are heavier. An interesting dichotomy emerged from the semi-structured interviews. Almost all women in the folliculogenesis sample used tampons. The liberal / conservative divide seemed to be reflected more strongly in the attitudinal differences between women who used tampons with or without applicators, than between those choosing tampons over pads. Tampons with applicators were favoured by those women who did not wish to touch their genetalia. The attitudinal differences between the women using the two sorts of tampon were not investigated here, but this apparent dichotomy might fruitfully be pursued in future.

More than half of women surveyed said that they did have or might have PMS. PMS was not defined for them, and no measure of severity was made, however, the rate of retrospective PMS reporting is within the variable range of incidence estimates given in the literature (eg. Asso, 1983). Women were asked if they experienced any of a large number of possible cyclic symptoms. The most commonly reported symptoms were physical, though tension and tearfulness were noted by more than half of the sample too. Bloating, breast tenderness, and period type pain were also the symptoms which showed the clearest evidence of cyclicity prospectively in the folliculogenesis sample.

In this sample women who do and do not take the pill reported experiencing PMS with a similar frequency. Yet there was a slight tendency for non-pill takers to indicate specific symptoms more frequently, suggesting that oral contraceptives may reduce the

severity or number of symptoms which a woman experiences. An alternative explanation is that more symptomatic women do not choose, or do not tolerate the pill (eg. Bancroft & Sartorius, 1991). Some sort of self-selection process of this kind may explain why pill takers do not report higher incidences of those symptoms which the combined pill has been traditionally linked such as depression, nausea, and headaches (eg. Mears, 1966).

4.9.2 Characteristics and Differences of Sub-samples

In addition to the general finding that this sample of FPC attenders has similar characteristics to population samples reported in other studies, it was clear that the sample of women who took part in the folliculogenesis study were representative of the larger population on all aspects measured. Equally women using different methods of contraception were also similar for the majority of factors, with a few notable exceptions.

Predictably, women using methods other than the pill were older, of higher parity, and not so often employed as pill takers. There may be a variety of reasons for these differences such as: the pill is less widely prescribed to women over thirty, age and parity are likely to be confounded, parous women have access to methods like the IUCD which are not generally offered to nulliparous women, barrier methods may be more likely than hormonal methods to be used post-partum or to space children, women with children may be less likely to be in paid work or have opportunities for advancement to top level jobs, etc.. Further, the decision not to use the pill may be linked to greater acceptance of a more traditional female role which has led some of these women to choose to be homeworkers and mothers.

The not surprising fact that more women using non-hormonal methods have heavy bleeding has been mentioned above. In spite of differences in bleeding experience, however, the two groups do not differ in their views of the importance and reasons for having bleeds. Between three and four out of five women, regardless of method used, seem to view bleeding in normative and practical terms. It is seen as a monitor of continuing good health and normality. While acting as a measure of contraceptive performance, it is nevertheless seen as a nuisance. The reasons given for the importance of bleeding by women in this sample are similar to the WHO survey (Snowden & Christian, 1983) which reported that a majority of women world-wide

consider bleeding " a natural, vital, physiological episode" which is "a sign of continuing youth, fertility and femininity", of non-pregnancy, and a cleansing of "bad blood". In this sample there was a tendency for women to relate more to the cognitive than the emotional concepts about bleeding (eg.-womanliness, cleansing) which may reflect a greater emphasis in Western culture on mechanistic, medical explanations of physical experience.

It is of considerable interest and importance to the interpretation of the findings in this thesis that women view their bleeding experience in a similar way, and endow it with the same meaning whether or not they use oral contraception. Withdrawal bleeding during pill cycles is physiologically different from menstruation. Yet a significant proportion of women wrongly believe that withdrawal bleeding is an accurate assurance that they are not pregnant, and even continue to see it as a sign of fertility when the express purpose of oral contraception is to suspend one's fertility. This belief structure undoubtedly influences women's willingness to undergo manipulations of their pill cycle length. Having said this, the fact that more pill takers have altered the length of their cycle in the past may reflect greater flexibility in their beliefs. Alternatively, it may simply indicate greater opportunity, since non-pill takers cannot exercise the control over the timing of their bleeds that pill takers may.

4.9.3 Attitudes to Bleeding

The most notable information to emerge from the semi-structured interviews was that women's beliefs about bleeding and their cycles are highly complex and characterized by ambivalence. The broad outline of women's beliefs about whether and why they consider bleeding important were discussed in relation to question 29 above. The questionnaire supplement offered more insight into the nuances of attitudes.

Brooks-Gunn & Ruble (1980) used a similar approach to the supplement in the Menstrual Attitudes Questionnaire which included 33 statements with which women could agree or disagree. The factors they derived from their investigation are similar to the themes which emerged from the interviews and were incorporated into the MHRAQ-2. These include the ideas that bleeding is natural and womanly, and it is probably wrong or dangerous to interfere with it. On the other hand, it is embarrassing, a source of shame, should be concealed, is messy, and is troublesome when it causes symptoms.

A majority of women surveyed conformed to the idea that bleeding is an embarrassing event which ought to be concealed, and were particularly worried by the idea of "excretory soiling". However, they did not seem eager to maintain the status quo, as most believe that both male and female children should be taught more openly about bleeding than they currently are. Otherwise most women in this sample subscribe to the view that bleeding does not affect them a great deal, and is generally a neutral experience. The men in their immediate environments are generally supportive, or at least not derogatory about their cycles.

One of the most deeply rooted menstrual behavioural restrictions is the taboo on sexual intercourse during bleeding. More than half of this sample reported abstaining from sex during bleeding, in spite of their apparently relaxed attitudes. This figure is consistent with other reports for "Western" women (eg. Paige-Eriksen, 1987; Matlin, 1987), while the sex taboo is reportedly observed by almost 100% of men and women outside the US and UK (Snowden & Christian, 1983). It is not clear why this behaviour persists. Women had great difficulty during interviews in offering plausible reasons for it. Many replies related to the stated "unclean" nature of menstrual blood and an implied fear of its dangerous, almost supernatural ability to defile those who come into contact with it. Interviewees were not able to articulate this concept directly, and questionnaire respondents gave the "mess" as their reason for abstaining. This deeply sublimated pollution belief may help to maintain the "traditional hierarchical relations between the sexes" (p. 185, Paige-Eriksen, 1987). Equally in some cases sex may be avoided because of physical discomfort and cycle-related loss of well-being during bleeding.

4.9.4 Attitudinal Differences in Sub-samples

It is somewhat surprising that pill and non-pill users, and volunteers and non-volunteers only differ subtly on measures of attitudes to bleeding. In the pill/ non-pill comparison the differences may be explicable in terms of higher parity and heavier bleeding amongst non-pill takers. If women on the pill have lighter, more predictable, and possibly less painful bleeds then they are likely to be less affected by them. Equally, the relative ease of their bleeds may mean that they require less support from their partners, while the non-pill user has had more opportunity to challenge the level of her partner's sympathy. Several authors note that heavier bleeding is related to greater

symptom experience, both before and during bleeding (Brooks-Gunn, 1985; Snowden & Christian, 1983; Paige, 1973). This fact would be consistent with the tendency for non-pill users to report more cycle-related changes. The pill and non-pill groups differed in age, and it is possible that a future age-matched comparison of pill and non-pill users might reveal more marked differences in bleeding-related attitudes than those found in this survey.

The ways in which those women who did and did not volunteer to take part in a study of altered cycle length differed seem to reflect differences in the strength, as opposed to the direction, of certain beliefs. In particular, volunteering women held less neutral views of bleeding, and were more inclined to link the effects of bleeding to greater pain and volume. Yet the groups did not differ in terms of these parameters. The only difference in symptom reporting was the incidence of food craving.

In addition, though all potential volunteers were similar demographically, there was a tendency for women who did volunteer to report more frequently that they experience PMS, and also to indicate that the pill had improved their PMS. Equally those women not volunteering were slightly more likely to suggest that they disliked the hormonal effects of the pill. Thus they may be put off a study in which cycle length is altered because they tend to have adverse reactions to hormonal interventions, or because they are less comfortable with the idea of such interventions.

These differences in current and past PMS experience have important implications for the further study of the effects of cycle manipulation on well being. It would be valuable if volunteers were inclined to have cyclical change in a study relating it to cycle length, however, if the sample has already experienced a hormonally mediated improvement in their PMS, then the potency of any manipulation effects will be proportionally diluted. The differences between the groups may reflect underlying personality differences which would also influence the data volunteers would generate in a future study. For example, the greater strength of their views may reflect greater extroversion, and an inclination to take part in a study in which they can further voice these opinions. PMS reporting, particularly retrospectively, has recently been linked to high neuroticism with a failure to confirm cyclical symptoms prospectively (Taylor, Fordyce & Alexander, 1991). If the study sample were more neurotic, and less likely to confirm this would have clear effects on findings.

It is interesting that the two groups of women did not differ in their past experience of cycle manipulation and that volunteers were only slightly more likely to express a willingness to do so in future. One would have expected this measure above all others to be predictive of volunteering. Indeed it is not clear from their responses to questions about attitudes why none of the 80% of non-volunteers who "would alter" their cycles failed to offer to do so.

4.9.5 Attitudes to Cycle Manipulation

Miller & Smith (1975) found that 79% of women in their white, unmarried, nulliparous, lower to middle class sample would *very likely* or *possibly* eliminate bleeding if it could be done safely for a time. The same question on the MHRAQ-2 more than 15 years later produced an almost identical distribution of responses, with about 4 out of 5 women saying they might alter their cycle. Jarvis & McCabe (1991) also found that 79% of their sample "would like to have their menstruation reduced".

When one women was asked in the semi-structured interviews if she would alter her cycle if she could. Her reply may explain some of the inconsistency in women's stated views:

> "I think I tend to think when you take it normally and have the pill free week you're actually having a normal period. I think in my mind it is as it was before, and will be the same when I come off it. Whereas if you kept taking it all the time *that would be taking a drug to stop having periods* [My emphasis]." (T8)

The overarching theme which emerges from the literature on attitudes, desire for cycle manipulation and the findings of the interviews and MHRAQ-2 is that both pill and non-pill taking women wish their vaginal bleeding experience to be regular and "normal". Instead of increasing the flexibility of women's concept of bleeding in fact, oral contraception has actually reinforced the false belief that the 28-day cycle is the norm. Because so many women take the pill, and the length of the cycle, at least with combined pills is so invariate, the "average" cycle length across all women is probably indeed nearer to 28 than it was before the pill was introduced. Further, the convenient predictability of the pill, sometimes foreseeable to a particular time on a given day in established users, seems to have made women intolerant of what are genuinely normal deviations in cycle length. Ironically, the recent history of hormonal contraception may be in large measure responsible for the lack of willingness on the part of women to pay

more than lip-service to the idea of extending their cycles. With hindsight it might have been better for women if the oral contraceptive pill regime had been completely different from the menstrual cycle from its inception, thus the belief structure that grew up around it might too have been more flexible.

4.10 Summary and Conclusions

This chapter indicates that the Family Planning Clinic sample from which all volunteers in this thesis were drawn is fairly representative of well educated, working women of reproductive age, and particularly of oral contraceptive pill users. It has also shown that women's beliefs about vaginal bleeding are complex, and not necessarily uni-directional. Cultural attitudes inform both how questions about beliefs and experience are posed and how they are responded to. While many women express a willingness to manipulate the timing of their bleeds, it is possible that they may not be so prepared to do so in practice because they are influenced by a desire to have "normal periods". Women who take the pill view their bleeds and their cycle-related experience very similarly to women who do not use hormonal methods.

Finally, the interview quote below highlights the danger of researching the menstrual or pill cycle without considering the social context in which it is experienced:

> I think there's a certain stigma attached to it still. It was just the reaction I had of a guy in the pub, and I didn't know him. I was with a friend and he knew my friend quite well. And he'd had a lot to drink, like he was pretty 'fou', and he turned round to my friend and he said, "Are you **bleeding** this week?!" and I thought 'Oh no, I'm going to punch this guy in the nose'. And she turned around and sort of looked at me and she said, "We'll go somewhere else". And I says, "Yeah, come on-let's get out of here." You know. Like it was just so silly, and it was obviously something that he thought 'Yeah, this is going to strike a chord, so I'll say to...', like it really was. (*Was that to be aggressive or...?)* Like everything you would associate with being bad. Like he was just doing this to hurt us. There is still a stigma attached to it. (*Taboo?)* Yeah, unfortunately, which is a little disappointing. Come on it is 1989!... (*So what did that guy mean?)* Well there is a sentiment attached to the fact that you're not **clean**. And people aren't so keen to have intercourse then- and certainly that he was better as us because he didn't bleed and we did!...Nasty, vicious, little man. You forget when you've got quite an informed attitude what the rest of the population is like. And to me that was the rest of the population rearing its ugly head in the worst possible form, to say something like that. (T9)

Chapter 5 The Development of an Experimental Model to Detect a Biological Rhythm of Well Being Using Clinical Case Studies

5.1 Introduction

In Chapter Three a possible aetiological explanation was considered for the persistence of cyclical change in emotional and physical well being during OC cycles. That study showed that if there is a relationship between changes in well being and fluctuating endogenous steroids it is probably weak, and is not adequate to explain the presence of cyclicity in low dose monophasic or triphasic pill cycles. Chapter Four dealt with women's attitudes to contraception and vaginal bleeding, and addressed the potential acceptability of a contraceptive regime that alters the frequency of vaginal bleeding. The interviews and questionnaire survey revealed that women's perceptions of their bleeding experience are complex. While 80% of questionnaire respondents expressed a willingness, in principle, to use a contraceptive that reduced the frequency of vaginal bleeding, the majority of women using OCs and other methods consider vaginal bleeding to be a sign of fertility, normality, good health and non-pregnancy, and disagree that it it unnecessary when using reliable contraception.

These investigations provide the background for the research reported in this chapter and the next by discounting one explanatory hypothesis and by elaborating the social context in which these questions must at all times be considered. This chapter focuses on the important temporal relationship between the steroid cycle and well being, and offers a new theoretical model to explain it, an infradian rhythm of well being. The nature of the purported rhythm was explored in the clinical setting of the Royal Infirmary of Edinburgh Premenstrual Syndrome Clinic.

Because the aetiology of PMS is so poorly understood and women's experience of the syndrome is so varied, effective treatment is difficult. The treatment strategy adopted in a clinical setting may have to be individualized and experimental to achieve the best result for a particular woman (Nader, 1991). From the Spring of 1988 until the Spring of 1991, Dr. John Bancroft and I saw a number of PMS Clinic patients with who were taking the pill. For many of these women Dr. Bancroft had chosen oral contraception as the first line of treatment for their PMS, while the others were already using the pill for contraception or PMS treatment at the time of referral to the Clinic. When I initially

became involved with the Clinic, Dr. Bancroft had just begun to explore the possibility that manipulating the length of the pill cycle, and in particular altering the timing of withdrawal bleeding, might have a therapeutic effect on adverse cyclical symptoms. Over the course of the next three years pill cycle length manipulations were attempted with about a dozen women in an effort to manage symptoms. These explorations helped to refine the theory and experimental model for an infradian oscillator. The outcomes of these single case studies and some features of the theoretical model are reported in this chapter.

5.2 Theoretical Background to Cycle Manipulation in the PMS Clinic

As with cyclical change experienced during the menstrual cycle, some women who take the pill feel worst prior to bleeding, while others have negative changes during bleeding. Some pill takers have symptoms which remit gradually over the bleed, while others experience an abrupt and dramatic improvement in well being coincident with the onset of vaginal bleeding. Many women experience the onset of symptoms during active tablet taking, therefore cyclical symptoms cannot be explained simply in terms of steroid withdrawal.

Figure 5.01 shows the profile of daily diary ratings for depression and bloating with bleeding, during two pill cycles for a PMS patient (code no. 8986) established on Microgynon. It is clear that both mood and physical symptoms have their onset before the pill steroids are withdrawn. It is also clear that the timing of symptom onset differs from one cycle to the next; both symptoms occur earlier in the second cycle than in the first. The occurrence of mood and physical changes and their remission during withdrawal bleeding, along with variable timing from one cycle to the next cannot be readily explained during the apparently constant hormonal conditions of the monophasic pill cycle.

The variety of temporal arrangements of symptoms which one sees in pill takers led Dr. Bancroft and me to postulate that there may be a number of specific ways in which altering the timing of pill taking may have a therapeutic effect on cycle-related change. We considered four potential causal mechanisms to explain the sort of responses observed which may be known as: 1) a 'menstrual release' factor, 2) an exogenous

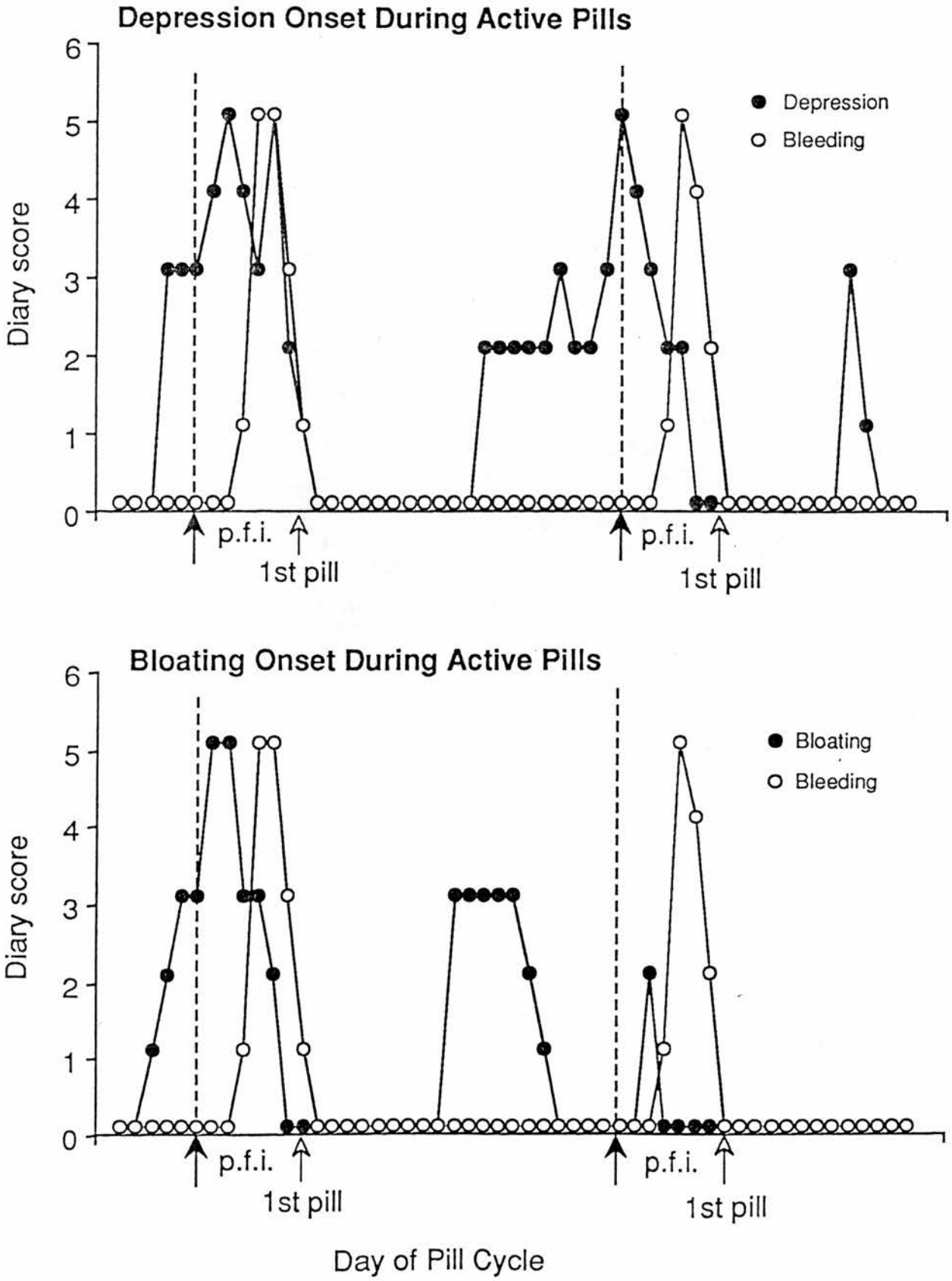

Figure 5.01 Profile of daily diary ratings for depression and bloating in relation to bleeding during two consecutive pill cycles in a PMS Clinic patient showing the onset of symptoms during active tablet taking, and the variable timing of symptom onset from one cycle to the next.

steroid withdrawal factor, 3) an endogenous steroid recovery effect, and 4) an endogenous infradian rhythm.

1) In the first case, "menstrual release", we hypothesized that those women who experience relief from symptoms with the onset of bleeding would benefit from a shorter cycle in which vaginal bleeding was advanced, as this might cut short symptoms. 2) In the second group of women, the withdrawal of pill steroids seems to be associated with symptom onset. The most obvious example of this is the case of 'menstrual' headaches. The normal clinical solution to 'menstrual' headaches is to extend pill taking beyond the conventional four week cycle (Guillebaud, 1991). This is usually effective in reducing the number of steroid withdrawal headaches which the woman has. Other symptoms may also occur predominantly during withdrawal bleeding. This led us to hypothesize that extended pill taking could have therapeutic potential by deferring symptoms in those women vulnerable to a steroid withdrawal effect.

3) We also considered the possibility that the symptoms which pill takers experience might be a consequence of the endogenous steroid recovery which occurs as a result of the pill free interval, low steroid dose and/or poor pill absorption. We hypothesized that if the subtle changes in endogenous steroids typically seen over the pill cycle were responsible for symptoms extended pill taking might relieve symptoms by abolishing all steroid cyclicity.

4) A final explanation for persistent cyclicity during pill cycles, which is not necessarily incompatible with other mechanisms described above, is that it is a function of an endogenous rhythm of mood and physical well being, allied to the steroid cycle. The pill cycle provides a model system in which it is possible to manipulate the timing of both the steroid cycle and vaginal bleeding. Therefore, by altering the length of the pill cycle one may attempt to disrupt the temporal relationship between the well being, bleeding and the steroid cycle.

5.3 Hypothesized Features of an Infradian Well Being Rhythm

We may make reasoned guesses about the characteristic duration, amplitude, etc. of the proposed rhythm which will help us to interpret it. First of all, it may be reasonable to

postulate that the length of the rhythm will approximate the length of the menstrual or pill cycle. Hypothetically, the length of the endogenous mood rhythm will be similar to the length of each woman's own central trend in cycle length (Treloar, et al., 1967), or perhaps entrained to the length of the pill cycle in long term users. One might also expect the freerunning period length of the infradian mood rhythm to show a good deal of inter, and intra-individual variability, as the length of a biological rhythm is "seldom very accurate" (p.191) and "[i]t is inherent in the variability of biological rhythms that the duration of a rhythm may differ from cycle to cycle" (Sollberger, 1965, p.203).

Another feature of this rhythm which might be expected to show large differences across individuals, is its amplitude. There is certainly no uniformity over women in the severity, nor even the features of cycle-related change. Therefore, one should expect equal variability in free running conditions. Given this, a further probable aspect of this rhythm is that it is a weak, and subdominant oscillator. If it were of prime functional significance to show circa-monthly cyclicity in subjective state and behaviour then the pattern would be more consistent across all women.

We hypothesize that the prime zeitgeber is the steroid cycle itself. While the feedback mechanisms involved in the sequential events of the menstrual cycle are now well understood, we do not possess an equal understanding of the mechanisms which time the system. Since cycles of well being persist during pill taking it is unlikely that the ovary is responsible for their timing. Yet their presence during pill cycles, with a timing and severity equal to the menstrual cycle (eg. Walker and Bancroft 1990; Yuk, Cumming, & Cumming, 1991) does imply that cycling steroids of either artificial or natural origin, may express some form of control over the infradian rhythm.

Further evidence of the infradian rhythm's "dependence" on the steroid cycle is the fact that it is largely absent before puberty, after the menopause, and during pregnancy[1]. This may imply that it is only partially endogenous. The severity of change in well being over the steroid cycle may depend on the close phase relationship of the two rhythms. Sollberger (1965) outlines a number of technical features of rhythms that may be of relevance here. He describes many components of the menstrual cycle as being of the relaxation oscillator type. A variety of common rhythm models, including

---

1
There are anecdotal reports of continued cyclicity in well being after menopause and during pregnancy (eg, Walker personal communication; Dalton, 1983; Kyger & Webb, 1972).

the relaxation oscillator, are reproduced in Figure 5.02.. The concept of a relaxation oscillator comes from van der Pol who described certain biological rhythms, such as the heart beat, as characterized by a slow accumulation of energy which is suddenly released when that energy is large enough to overcome a certain resistance in the system. After this release of energy there is a 'refractory period' during which energy is re-accumulated. The outcome is what Sollberger terms a characteristic "saw tooth pattern" over time.

Examples of relaxation oscillators in the menstrual cycle are the gradual development of a dominant follicle which suddenly ovulates in response to a transient LH surge, and the slow build-up of the endometrium which rapidly sloughs off at menstruation. The cyclic change in well being which many women experience over the steroid cycle may fit this type of oscillator model. Negative affect and physical changes may develop gradually over the second half of the cycle reaching peak severity a few days before or immediately prior to menstruation. Some women then experience immediate relief from symptoms with the onset of bleeding, while for others it is more gradual over the course of bleeding.

The idea that biological rhythms may be hierarchical was discussed in Chapter Two. Rhythms may simply be superimposed on one another, or may actually modulate one another's behaviour (see for example combined impulse and sine wave model, Figure 5.02). In wave theory, "superposition" is a phenomenon whereby waveforms that are superimposed on one another become mathematically additive. Sollberger (1965) argues that when relaxation oscillators are 'lined up', or coupled this synergy is particularly pronounced. Thus an infradian rhythm of well being which is relatively innocuous on its own may only become noticeable, or troublesome when it is coupled with the steroid cycle.

Two rhythms which are internal to the organism, the steroid and well being cycles here, may interact with one another to establish a coupled oscillator condition. If one is dominant to the other, the "leading" oscillator, (the steroid cycle) then it is called the "pacemaker", as it gives 'time' to all its subordinate oscillators (the mood rhythm). When the system is disrupted and the coupling disappears, the rhythms then begin to oscillate at their respective characteristic frequencies (Sollberger, p.180). If the

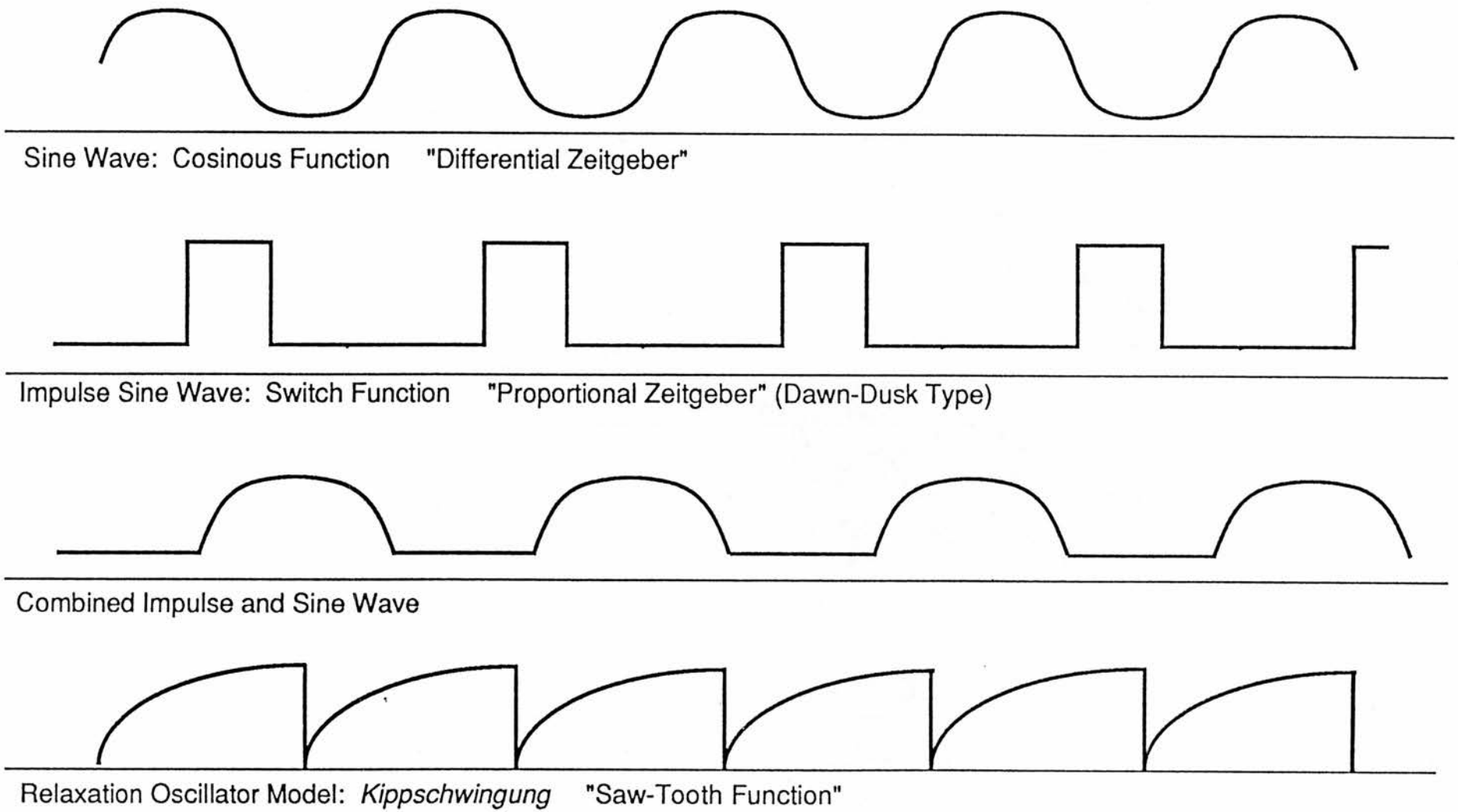

Figure 5.02 Schematic of a number of common models of biological rhythms taken from Sollberger (1965), p.14.

coupling is "multidirectional" then the relationship between rhythm phases is much more complex.[2]

5.4 Methods of Assessment

Women are referred to the PMS Clinic at the Royal Infirmary of Edinburgh by their General Practitioner, their Gynaecologist, other clinics, or by themselves. At the time that a woman is enrolled at the Clinic she is required to keep a daily diary record of her mood and physical well being for two complete menstrual or pill cycles. She is usually also requested to collect thrice weekly early morning urine samples for hormone assay. These samples are assayed for oestrone-3-glucuronide and pregnanediol-3-glucuronide to relate the timing of symptoms to ovulation and the luteal phase, for example, to detect anovulation or luteal insufficiency. Pill takers are not generally required to collect urine samples. However, a number of the women whom I followed through the Clinic did collect urine given my interest in endogenous steroid production during pill cycles.

The Clinic diary contains twelve, six-point ordinal scales of mood and physical states commonly experienced over the menstrual cycle (see Appendix 5.01). Some print runs of the diary also include a thirteenth scale: "craving for sweet foods". Like the visual analogue diary described in chapter three, this diary also provides two spaces for additional scales to be added by the woman herself. Diaries are presented in the form of weekly booklets. This form of the daily diary has been used successfully in the PMS Clinic for a number of years (5+). It is shorter and simpler to complete than the diaries described elsewhere in this thesis, and therefore appropriate for clinical use. Urinary steroid assays were carried out using the ELISA techniques described in Chapter Three.

As far as possible, women were requested to maintain diary and urine collection during pill cycle manipulations. However, in practice diary keeping tended to be somewhat patchy. So where diary data and hormone results are available they are included to illustrate women's responses to particular cycle alterations.

2
If the coupling between the steroid cycle and an infradian rhythm were multidirectional then this might explain how the timing and therefore function of the steroid cycle is disrupted during extreme psychic stress.

Women were seen at the PMS Clinic at approximately one to six month intervals. The interval between appointments depended on the course of treatment. During the times that women were undertaking pill cycle manipulations, especially when these were first being established, visits tended to be monthly. Once established on a helpful cycle length, women were seen less frequently, particularly if doing well on extended cycles.

5.5 Results: Case Histories from an Edinburgh PMS Clinic

With no prior experience of the effects which cycle manipulations would have on well being, but with a number of hypothesized mechanisms, Dr. Bancroft and I systematically altered the length of the pill cycle in eleven PMS Clinic attenders. A detailed case report for each woman is contained in Appendix 5.02, and Tables 5.01 and 5.02 summarize their experience.

The three sorts of change made to the conventional pill cycle were: 1) long extensions of three or more additional weeks of active pills (n=6); 2) brief extensions of one to two additional weeks of active pills (n=2); and 3) shortening active pill taking by up to six days, with or without shortening of the pill free interval (n=3)[3]. Some examples of these manipulations are shown in Figure 5.03.

3
Short cycles are less versatile than long cycles as one may only shorten the active pill phase by a limited number of days and still achieve adequate suppression of gonadotrophin and steroid production. It is therefore more risky to use these manipulations in women who require the pill for contraception.

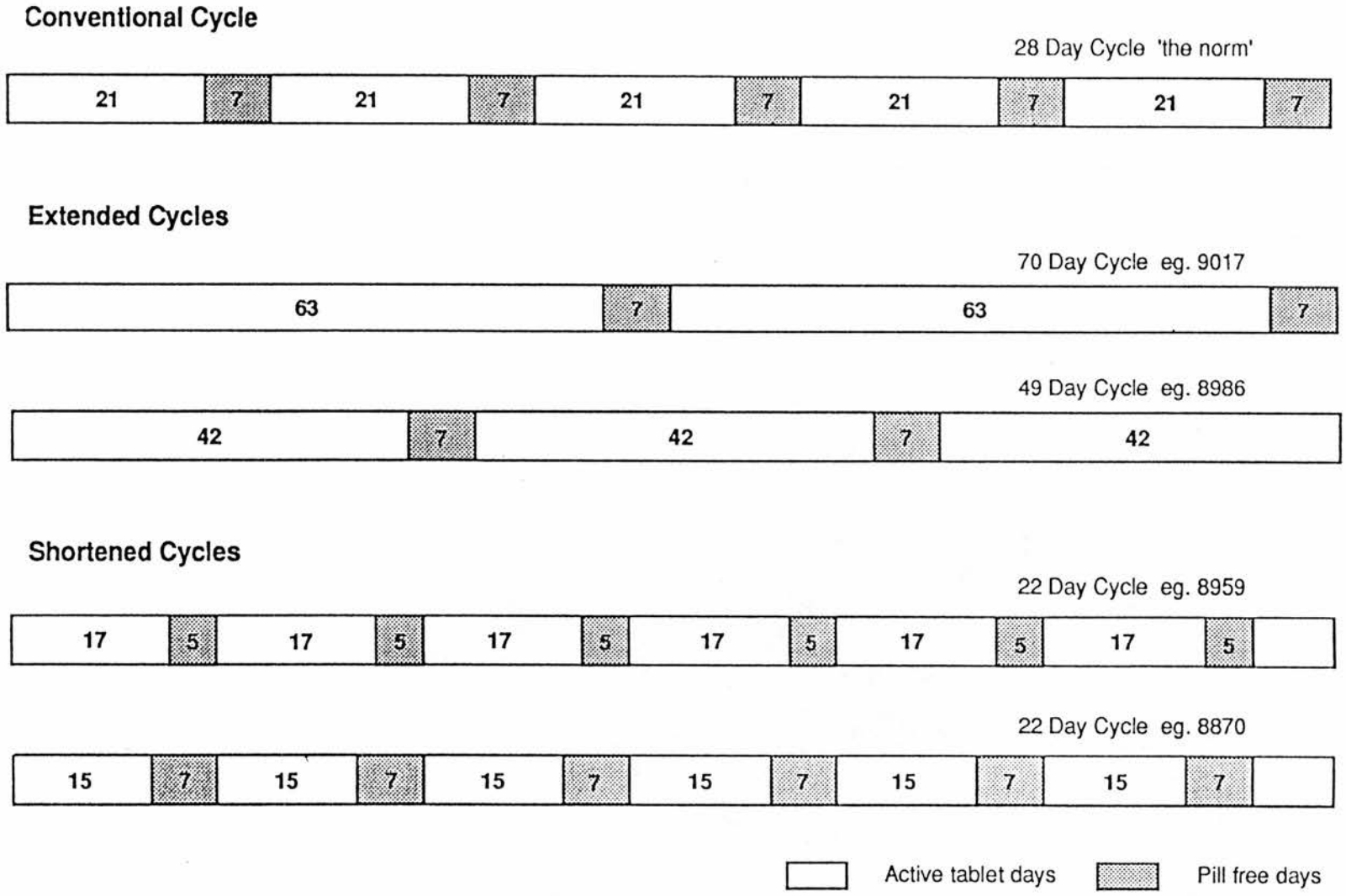

Figure 5.03 Examples of manipulations made to pill cycle length in women attending an Edinburgh PMS Clinic.

Table 5.01 PMS Patients in whom Pill Cycles were Lengthened for Treatment

Code No.	Pill Formulation	Cycle Manipulation/s	Outcome of Manipulation/s
8735	Ovran 30	1) 9wks+7dy pfi (twice)	general improvement of symptoms in cycle 1, but negative mood & bloating from wk 6 chronically until pfi in cycle 2
		2) 6wks +7dy pfi (once)	mood declined in wks 3-4 and wk 6 prior to the pfi
8804	Microgynon	6wks+7dy pfi (once)	breast tenderness, period pain, & irritability chronically from wk 4 until the pfi
8843	Microgynon	12wks+7 dy pfi (once)	moods generally improved, but still had 'bad times', breakthrough bleeding from wks 10-12
8846	Microgynon	9wks+7dy pfi (once)	migraine wk 4; chronic breast tenderness from wk 4; migraine, depressed and tearful wk 6; stopped pill early-wk 7; migraine 3 days later, migraine 15 days after stopping pill
8986	Microgynon	6wks+7dy pfi (6 cycles, ongoing)	general improvement in symptoms, but transient tension, anxiety, etc. mid long cycle
9017	Marvelon	9wks+7dy pfi (4 cycles, ongoing)	general improvement in symptoms, PMS less marked, but symptomatic at times of would-be bleeds in wks 4 & 8, main symptoms for ten days prior to withdrawal bleed
8868	Ovran 30	4wks+6dy pfi (once)	reduced severity of symptoms premenstrually, but depressed in wk 1 of next cycle after pfi
8927	Marvelon	1) 4wks+ 7dy pfi (once)	slightly improved; more irritable, but less depressed
		2) 5wks+ 7dy pfi (once)	severe period pain and very irritable in wk 5, but no bleeding

Legend- pfi= pill free interval in days, No.) = refers to the different sorts of manipulated cycles which a woman consecutively underwent. For those women who only experienced one type of manipulation the duration of treatment is noted in parentheses. Comments on the outcomes of manipulations are based on retrospective reports recorded in the Clinic notes.

Table 5.02 PMS Patients in whom Pill Cycles were Shortened for Treatment

Code No.	Pill Formulation	Cycle Manipulation/s	Outcome of Manipulation/s
8870	Microgynon	1) 15dys+7dy pfi (for 18 mos.)	PMS symptoms of anger and tension reduced from 3mos. to 2-3 days
		2) 4wks+7dy pfi (ongoing)	symptoms gradually returned to longer duration of 10 days pre-bleed, so she returned to conventional cycle
8959	Brevinor	1) 6wks+7dy pfi (once)	symptomatic at time of would-be bleed in wk 4
		2) 17dys+5dy pfi (3 cycles)	2-3 days depression and anger before bleed
8972	Marvelon	17dys+4dy pfi (3 cycles)	symptoms relieved in cycle 1, 1 day depression and tearfulness before bleed in 2nd cycle, but severe anger and depression after 2nd pfi

Legend- pfi= pill free interval in days, No.) = refers to the different sorts of manipulated cycles which a woman consecutively underwent. For those women who only experienced one type of manipulation the duration of treatment is noted in parentheses. Comments on the outcomes of manipulations are based on retrospective reports recorded in the Clinic notes.

5.6 Discussion of Trends

Women's responses to these manipulations have been varied. Similar regimens have not necessarily produced the same effects across women. There were two predominant sorts of responses to the lengthened cycles. Some women found that all or certain symptoms became chronic with protracted pill taking. In particular, breast tenderness, bloating, period pain, and irritability were noted to begin at the time of the first "missed" premenstrual or menstrual phase and then continue until relief was finally gained from steroid withdrawal bleeding in the pill free interval (eg- 8804). Other women found that negative moods and physical changes continued to occur at roughly monthly intervals, or when they otherwise would have appeared during the conventional four week cycle, and that these spontaneously resolved without the need for a bleed (8843, 8986 and 9017). In some cases the same women experienced both

the chronic and the cyclic patterns with different symptoms (eg. 8735 and see breast tenderness vs. depression for 8846 in Figure 5.05). Thus, both subjective mood and physical well being tended to continue to oscillate cyclically at roughly monthly intervals, or to become chronic in this group of women undergoing much lengthened cycles.

How do the outcomes fit in with the models described above for those cases who underwent prolonged pill taking? All those women in whom pill taking was extended had previously been experiencing their worst moods and physical changes after active tablets had been stopped, and during withdrawal bleeding. Therefore, it seemed superficially that they were responding to the withdrawal of exogenous steroids, and we would have expected them to benefit from less frequent steroid withdrawal. Yet, in the face of chronic steroid administration at a constant dose, they became symptomatic. One might propose that this resulted from the effects of chronic steroid administration, were it not for the fact that some symptoms spontaneously resolved in a number of women with no apparent change in the steroid environment.

Figure 5.04 shows the diary ratings for selected variables over 28 weeks for patient number 9017. She believed that an extended ten-week cycle vastly improved her moods, but that she still experienced some symptoms in mid cycle. This pattern is not very clearly reinforced by her diary ratings, although there does seem to be a peak in tension soon after her first 'missed bleed' in the first long cycle.

Patient number 8846 illustrates the complexity of women's reactions. She was started on the pill to control menstrual migraine headaches which she had experienced with menstrual bleeding since puberty. Dr. Bancroft reasoned that if her pill cycle was made longer than her fairly regular, approximately monthly menstrual cycle, then she would experience the headaches less frequently. However, while attempting a ten week regime she continued to have migraines at regular intervals during the pill cycle, although her endogenous steroids were well suppressed and she was taking the pill continuously (see Figure 5.05). Meanwhile, in the same steroid environment other symptoms reacted differently. Her breast tenderness instead of occurring cyclically was chronic from about the fourth week of pills, while depression and tearfulness, which were not changes she typically experienced, coincided with her second migraine attack during pill taking. And indeed, once she stopped taking the pill altogether she experienced two further migraines in rapid succession.

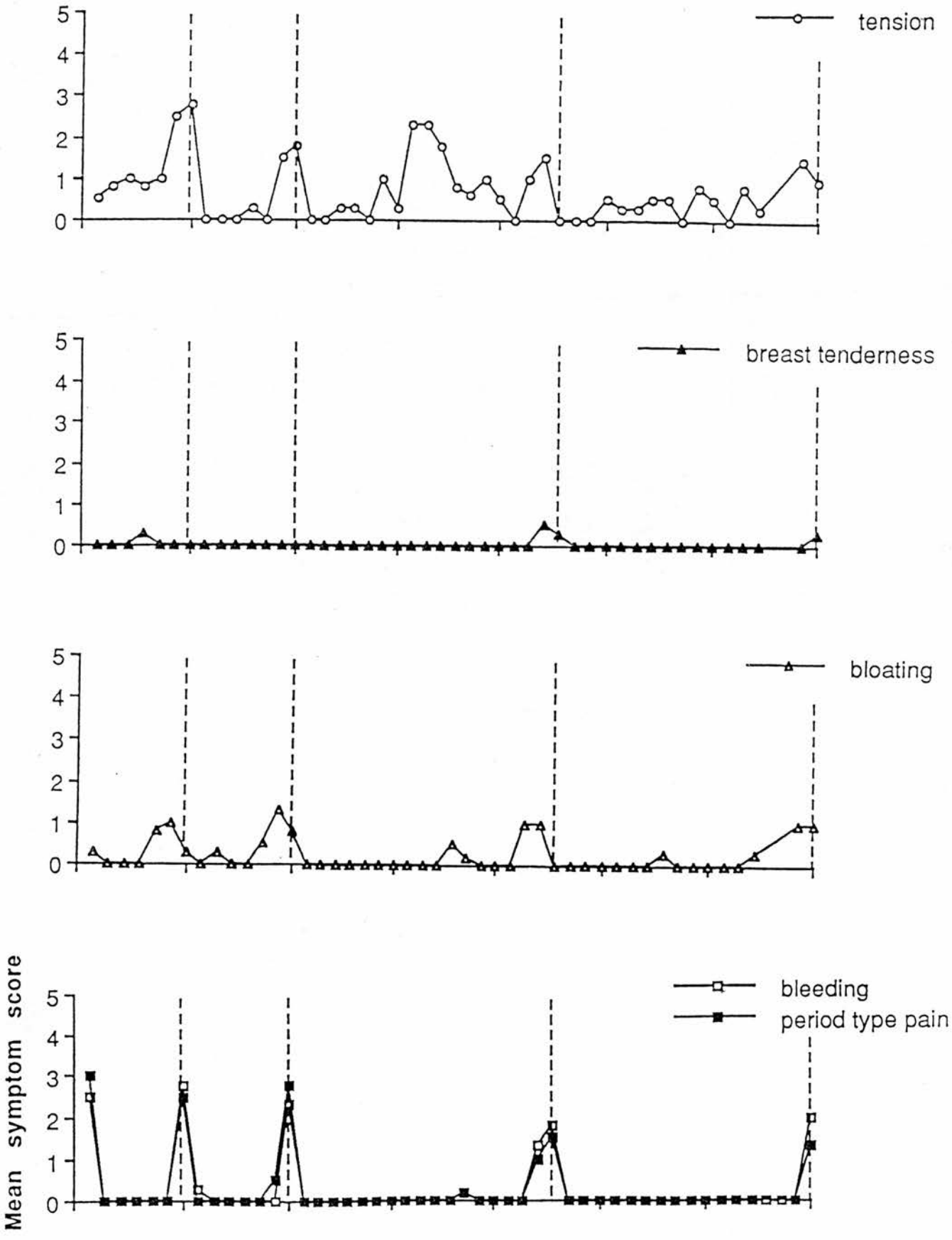

Figure 5.04 Four day mean phases for selected daily diary ratings of patient 9017 over two conventional pill cycles and two lengthened ten week cycles. Dotted lines represent the beginning of withdrawal bleeding episodes.

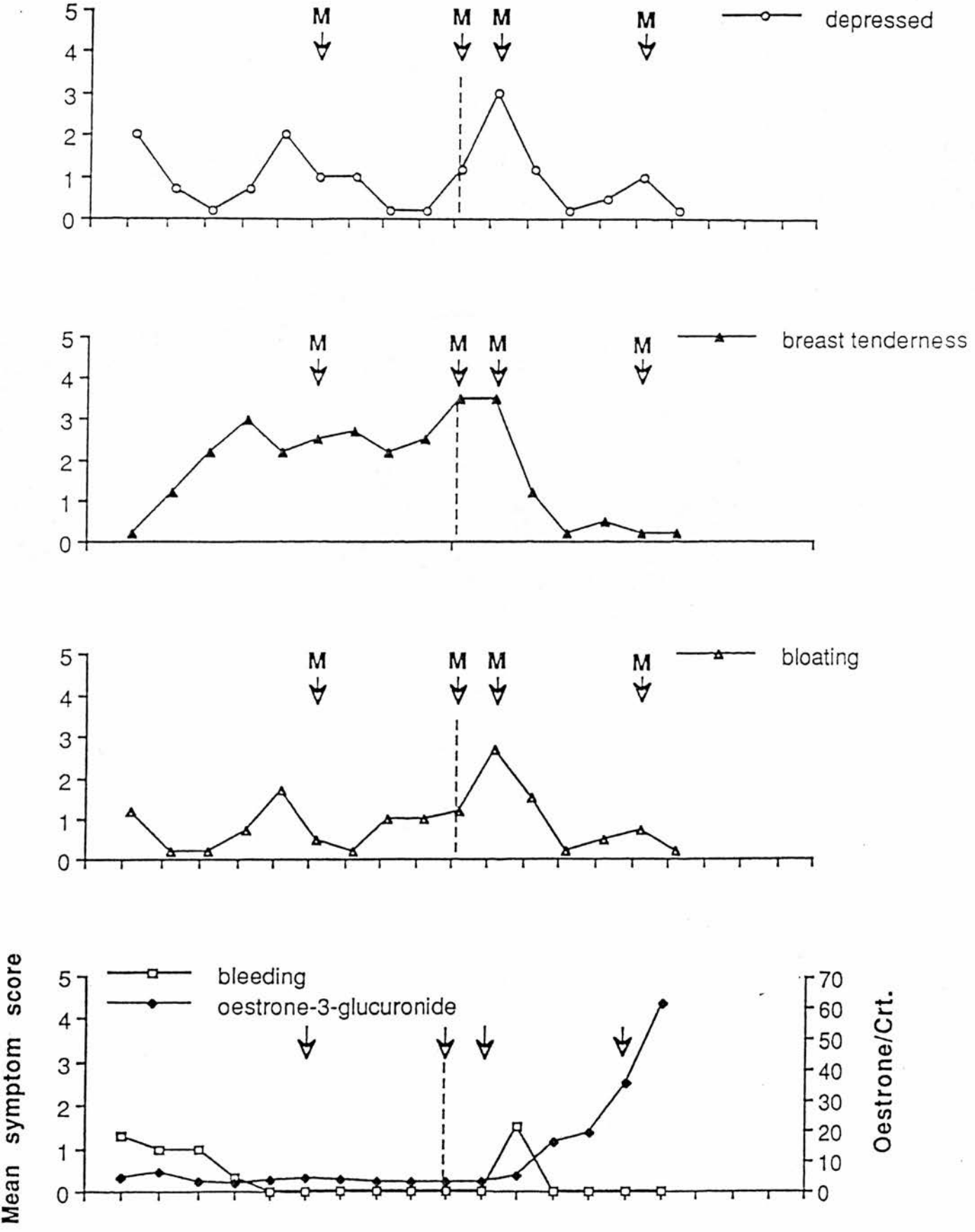

Figure 5.05 Four day mean phases for selected daily diary ratings of patient 8846 over one lengthened pill cycle. Arrows indicate the timing of migraine headaches. The dotted line indicates the onset of withdrawal bleeding when the patient stopped taking OCs.

In some way the disruption of the length of the steroid cycle, or of the steroid environment produced by this extended pill cycle, induced more frequent migraine. The pattern of her experience cannot be explained by "menstrual" release or by the withdrawal of exogenous steroids, as she was taking the pill constantly when she became symptomatic; nor can it be explained by the presence of endogenous steroids as they were basal in her case. From the four models, this leaves only the possibility that her migraine cycle was showing some endogenous rhythmicity, which had formerly been linked to the menstrual cycle, but which continued to oscillate when the length of the steroid cycle was artificially extended. Indeed five out of six of the women with protracted pill taking returned to the Clinic reporting the cyclical experience of at least some symptoms in the presence of constant pill taking. Four of these five women reported that the extended regime had reduced the severity of their 'PMS' although it had not abolished cyclicity altogether. Some evidence for this is given in Figure 5.06 which shows a slight rise in irritability and depression around the time of a 'would-be' bleed for patient number 8986.

In both women, who underwent slightly lengthened cycles, symptoms occurred at their usual premenstrual time, but were less severe, and then occurred again in about the fifth week since the last bleed. It is difficult to explain these effects in terms of any of the four models we have outlined. In one case (8868) the woman was depressed after a delayed six day withdrawal phase, while the other woman (8927) had her PMS-type symptoms in the fifth consecutive week of pills without a break. The two women were in hormonally distinct phases of their cycle, yet both became symptomatic at the same interval since the previous bleed. Both women had previously experienced their symptoms for about two weeks premenstrually and during bleeding. For 8868 the week when symptoms occurred would have been the early premenstrual phase of the next cycle, while for 8927 the symptomatic phase would have been the immediate post-bleeding week. Neither menstrual release, endogenous steroid effects, nor exogenous steroid withdrawal can explain their responses over time. Perhaps under differently timed entraining influences the endogenous pattern is emerging in these two women.

The reactions of the three women who underwent shortened pill cycles seem more clear. Similar to the group undergoing extended cycles, they showed two sorts of response. In two women bringing bleeding forward produced early symptom relief in the manner we had anticipated with a 'menstrual release' factor. Figure 5.07 shows regular oscillations in mood and physical changes over repeated short cycles for patient

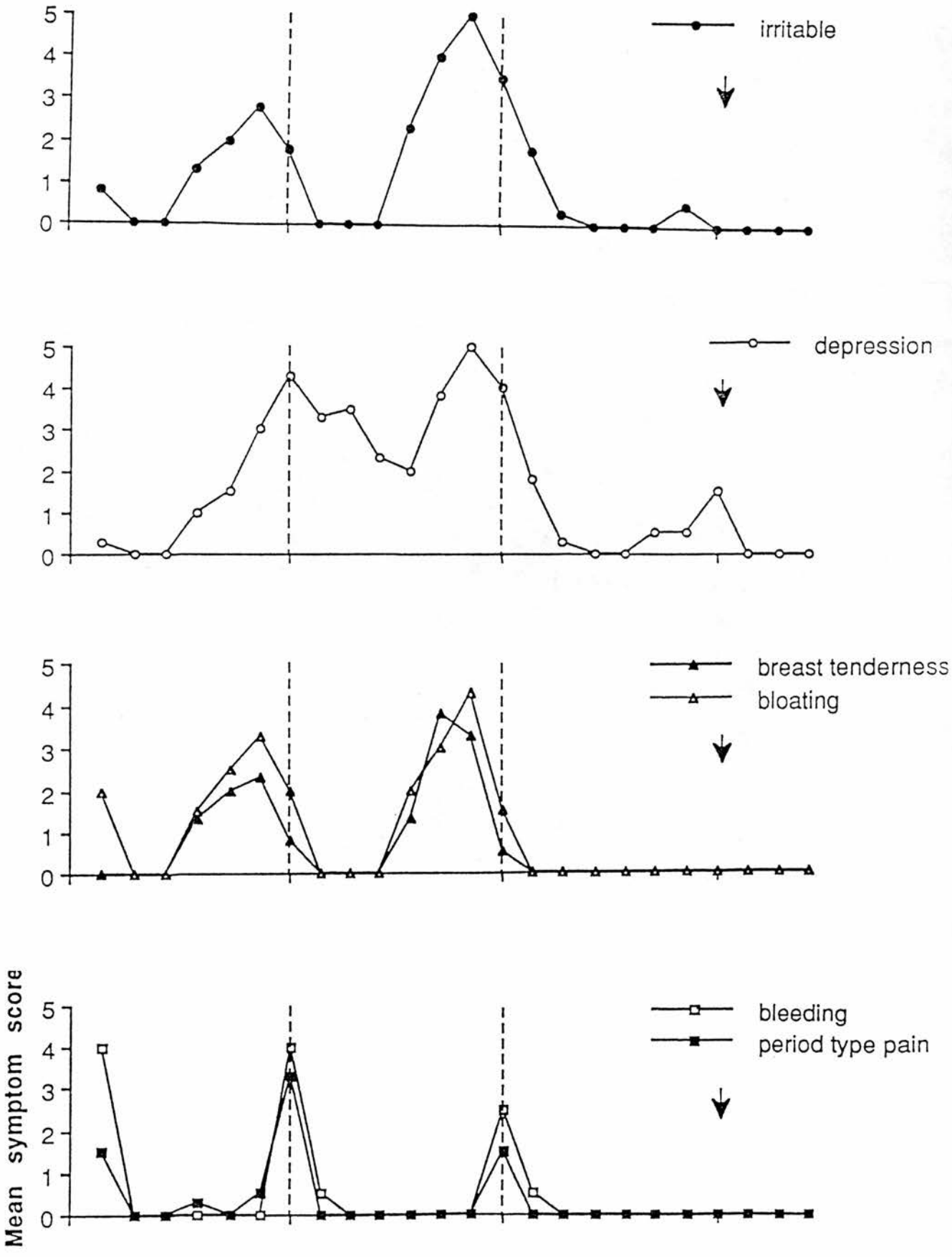

Figure 5.06 Four day mean phases for selected daily diary ratings of patient 8986 over two conventional pill cycles and the first six weeks of one lengthened pill cycle. Dotted lines represent the beginning of withdrawal bleeding episodes.

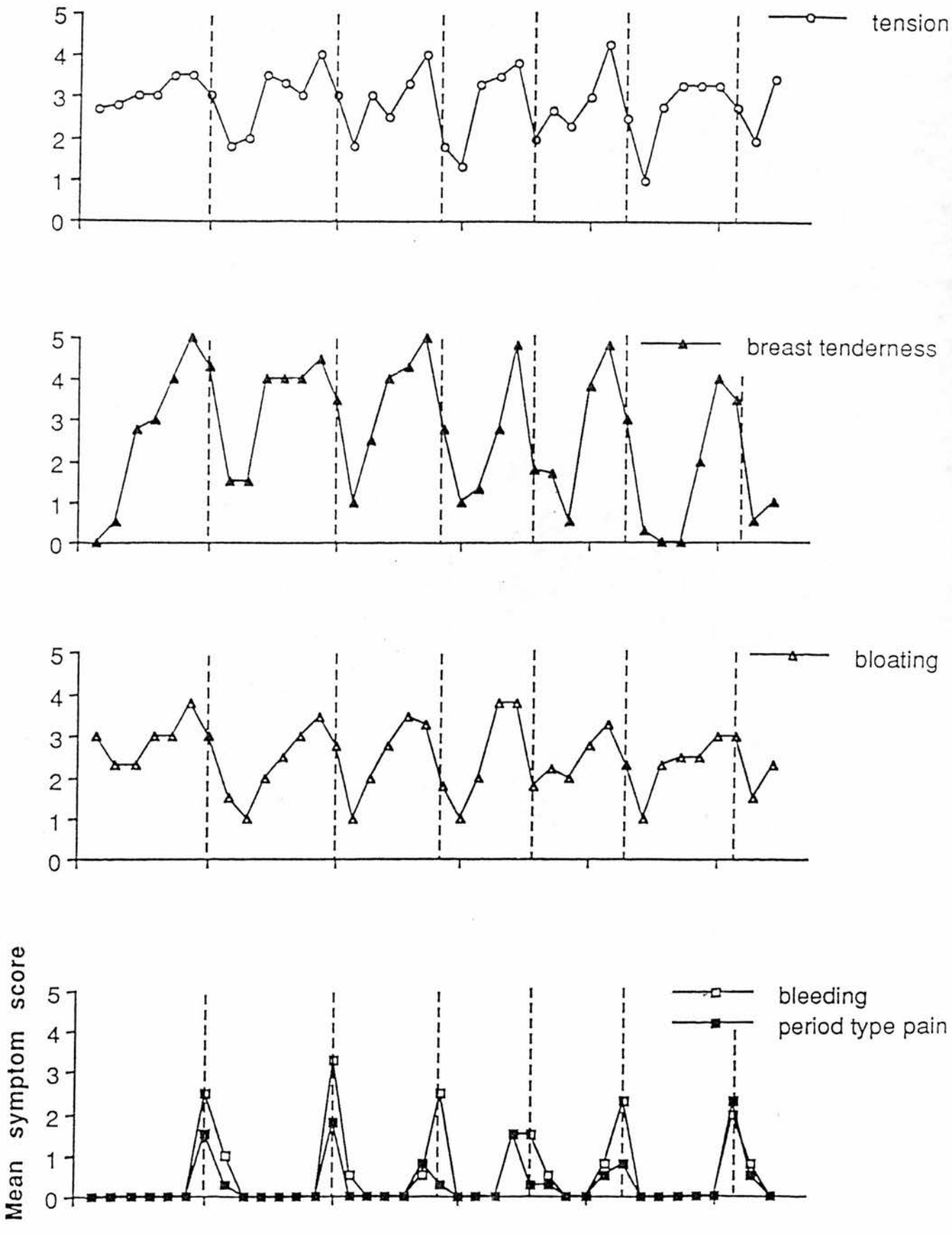

Figure 5.07 Four day mean phases for selected daily diary ratings of patient 8870 over two conventional pill cycles and four consecutive 22 day pill cycles. Dotted lines represent the beginning of withdrawal bleeding episodes.

number 8870. She seems to experience the overall pattern of symptoms, but for less time. The third woman reported experiencing 'post menstrual PMS'. The response she described was similar to that of women in whom luteal regression was prematurely induced with RU486 (Schmidt et al., 1991), and may indicate the effect of an endogenous rhythm of well being. Her diaries show less clear evidence of cyclicity than 8870's, but Figure 5.08 suggests that she feels anger after her first and third short-cycle bleeds.

5.7 Limitations of the Clinic Data

The reactions of women to manipulations of their pill cycle length have been varied. Yet a number of trends in response have emerged from the small number of manipulations which we have tried in the PMS Clinic. While these trends are suggestive, it is difficult to draw any firm conclusions about the mechanisms which might be responsible

This anecdotal clinical data set has a number of limitations. Cases were accumulated slowly over a long period of time. A trial-and-error approach had to be adopted because we had no prior experience of the indications or outcomes of these temporal regimes. Thus the protocol followed with each woman was individualized. As we gained in experience, we refined our procedures and the gradual evolution in our thinking about these treatments meant that no single protocol was rigourously followed over time.

These treatments were also not blind, nor were they controlled. Most treatments for PMS show a significant placebo effect (e.g Hamilton et al., 1988), and yet it is impossible to quantify the contribution made by womens' expectation that the manipulations would make them feel better. Indeed, we cannot discount the possibility that those women who showed continued evidence of cyclicity did so because they expected symptoms to occur at particular time intervals.

These women were also using a variety of different pill formulations, which seem *de facto* to produce different patterns of well being in different individuals, even during the conventional cycle. Finally, women could not be required to collect diaries and samples indefinitely. They were attending the Clinic foremost as patients requesting

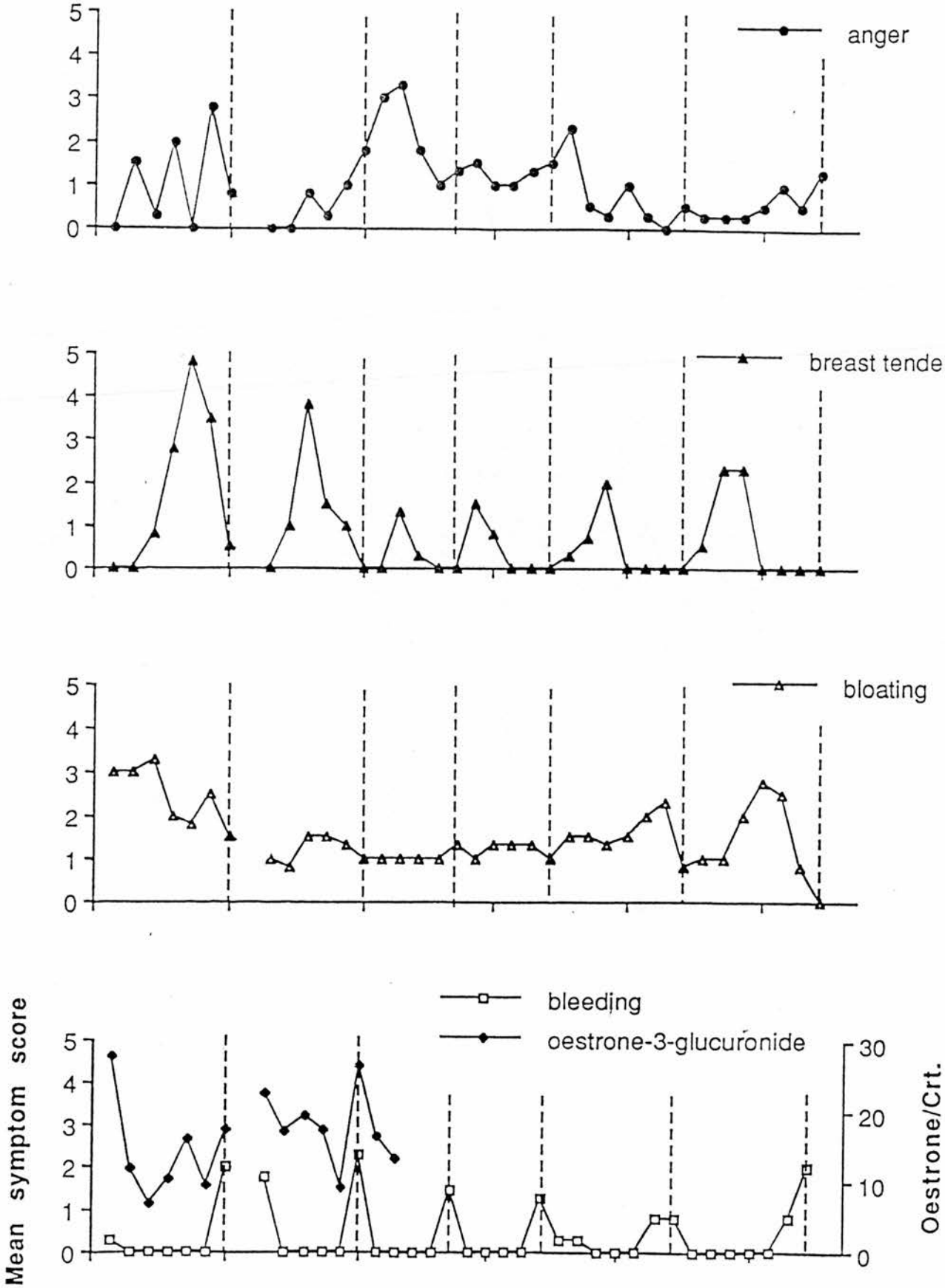

Figure 5.08 Four day mean phases for selected daily diary ratings of patient 8972 over two conventional pill cycles, two consecutive 21 day pill cycles, and two more conventional cycles. Dotted lines represent the beginning of withdrawal bleeding episodes.

treatment, and not to provide data for a research project. Therefore, the diary data is incomplete and cannot be entered into rigourous mathematical analyses.

5.8 Implications for a Controlled Study to Test the Existence of an Infradian Rhythm

Albeit suggestive, there is evidence from the PMS Clinic treatment case studies that both mood and physical well being have the power to continue to oscillate in a constant or truncated steroid environment. An endogenous infradian rhythm is an appealing concept since it offers a plausible aetiology of cyclical change, and can also account for inter and intra-individual variation in its expression.

Five of the 11 women who underwent manipulations in the Clinic reported some degree of improvement as a result. However, this was only sustained for two women. One (9017) pursued 10 week cycles, and the other (8870) short 22 day cycles. Many of the remaining women actually discontinued the pill soon after trying an altered cycle length. All of the women who had lengthened cycles reported the persistence of either cyclical or chronic symptoms. It is interesting that the therapeutic lifespan of beneficial effects seemed to be finite. One of the few women undergoing shortened cycles illustrates this phenomenon clearly.

8870 was oligomenorrheic and experiencing three to five months cycles when she first came to the Clinic. Her symptoms tended to build-up from about two weeks after a period until relief finally came with the onset of the next period. So she was started on the pill in an effort to increase the frequency of bleeding and improve her PMS through a menstrual release mechanism. Twenty-eight day cycles did cut short prolonged negative moods and physical changes, yet she remained symptomatic for about two weeks prior to bleeding. She started short cycles because she wanted to relieve her negative mood early before a holiday, and asked if she could stop the pill on day 15 to see if this would help.[4] The 22 day cycle further abbreviated her 'bad phase'. She continued with short cycles, having only about 3 days of negative mood and physical discomfort before the withdrawal week in each cycle. She followed this regime for 18 months, over which time the duration of the "bad phase" gradually increased to about 10 days. She therefore returned to a conventional pill cycle.

4
She was sterilized, so did not need OCs for contraception.

There is good evidence in biological rhythm research that humans adapt differently to phase advances and phase delays (Désir, van Cauter, Refetoff, Fang, Goldstein, Fèvre-Montage, L'Hermite, Robyn, Jadot, Szyper, Spire, Noel & Copinschi, 1983). Aschoff called this phenomenon "reentrainment by partition". In his pioneering research on human circadian rhythms he determined that phase delay, or rhythm postponement (eg.- lengthened pill cycles) is much easier to adjust to than phase-advance (eg.- shortened pill cycles) (Edlund 1987). When the phase of a rhythm is brought forward it is more difficult for the organism to maintain the synchronization of its internal rhythms. For example, westbound air travel (eg. UK to USA) is associated with more rapid adjustment to the new time zone and less jet lag than eastbound. Pt. 8870 effectively underwent a radical phase-advance when she began a 22 day pill cycle after normally having about four month long menstrual cycles. The slow return of a longer 'bad phase' seems to reflect retarded reentrainment after a profound disruption.

"Reentrainment by partition" may also explain how it is possible that pt. 8972, and the women in Schmidt et al.'s (1991) RU486 study apparently show 'postmenstrual' PMS. The difference in individual responses may reflect the fact that for 8870 vaginal bleeding encourages entrainment in a way which it does not for 8972. Thus more than one entraining influence may be at work with variable potency in different individuals. It would be very interesting to monitor a large number of women in whom menstrual or withdrawal bleeding was phase advanced over numerous cycles to assess the degree and speed of entrainment to the new cycle length.

Women who seek medical help for PMS may be different from other women who have cyclical changes, but do not consult a doctor. Clinic patients may have greater faith in medical remedies and thus may be more susceptible than a study population to placebo effects (Warner, 1989- personal communication). However, this does not seem to be borne out by these data, because only a small proportion of the 11 found the manipulations helpful. From this data, the usefulness of cycle manipulations for treating PMS appears to be limited. Much more research is required before treatment strategies can be rigourously implemented.

A controlled, blind investigation is required in order to verify the existence of a proposed endogenous rhythm of well being and characterize its features. This study might explore a number of questions. If there is such a rhythm will it emerge under

"free running conditions"? How robust is it over time? What is its average phase length? Will it retain a consistent amplitude over time or will it become damped down? How much individual variation is there? Will different women show different phases and amplitudes? Does a woman's free running rhythm approximate her own underlying central trend in menstrual cycle length? How susceptible would such a rhythm be to the disruption, and re-timing of its primary zeitgeber? Is the steroid cycle its primary zeitgeber, or a coupled oscillator? Are there therapeutic gains to be made by "aligning" pill cycle length with "underlying cycle length"? And do parameters of physical and emotional well being show similar or different rhythmic characteristics?

5.9 Hypotheses to be Tested in the Controlled Study

The low dose combined oral contraceptive pill was chosen as a tool to pursue these research questions for a number of reasons. OCs eliminate ovulation and, to a large extent, the cyclic variation of endogenous steroids and gonadotrophins. Exogenous steroids are re-introduced in a controlled and easily manipulated way providing a simple, cheap, readily available, safe, and non-invasive means of changing the duration of the steroid cycle. Further, changing the length of the pill cycle is a familiar concept to many women. As discussed in the previous chapter, many women alter their own cycle length for reasons of convenience, which may include the control of cycle-related change in well being. Thus, the effects that cycle manipulations have on vaginal bleeding experience, and the acceptability of such changes to women may be considered concurrently.

The study described in the Chapter Six was designed to test three specific hypotheses relating to: 1) the existence of a purported endogenous mood oscillator, 2) the relationship of said rhythm to the steroid cycle, and 3) the symptomatic features of the rhythm.

1) If there is an endogenous infradian rhythm of mood which is normally entrained to the cycle of ovarian hormones it will continue to show periodicity if the temporal and hormonal inputs are held constant by continuous pill administration. Therefore:

H1: A group of women who undergo constant pill administration will show a regular oscillation of mood during the manipulation period which represents the free-running phase of their infradian mood rhythm.

2) If there is an endogenous infradian rhythm of mood which is normally entrained to the cycle of ovarian hormones then by lengthening one pill cycle we may achieve a "phase advance" or forward shift in the mood cycle relative to the steroid cycle. We will call this the "jet lag effect" because it should mimic the internal desynchronization of the various circadian period rhythms which one sees after long distance air travel. First there will be a disruption of the rhythms' relationship to one another, and gradually over subsequent pill cycles, the mood rhythm will become re-entrained to the hormonal cycle. Therefore:

H2: A phase-shift in pill taking will demonstrate that the hormonal cycle is a primary zeitgeber for the endogenous mood rhythm, as a temporary lengthening of the pill cycle in turn disrupts and re-entrains the mood rhythm to it.

3) If the driving force for changes in bodily state over the pill cycle is hormonal, and the driving force for changes in mood state is an endogenous period rhythm, then physical changes should vary in direct relation to fluctuations in endogenous and exogenous reproductive hormones, while mood changes should persist regardless of hormonal status. Therefore:

H3: Physical state will vary in direct relation to the specific hormonal changes induced by different pill taking regimes, while variations in mood state may occur independently of hormonal changes over time.

The rational behind the first two hypotheses was thoroughly discussed at the beginning of this chapter, but the third hypothesis has not been so explicitly considered. There is evidence that seems to suggest that the emotional and physical correlates of the menstrual or pill cycle are not controlled by the same mechanism. Bancroft & Backstrom (1985) propose a "systems model" to describe the probable causes behind PMS. They suggest that physical changes like breast tenderness and bloating are a function of the peripheral effects of cyclical steroids, while mood changes are produced by the central regulatory system.

In their 1987 study of the effectiveness of the LHRH agonist, Buserelin, for the treatment of PMS, Bancroft et al. found that for women who underwent extended agonist administration, but still had bleeds, physical symptoms continued to precede

bleeding, while the timing of mood symptoms became dissociated from the pattern of bleeding. And in light of the fact that physical changes associated with the menstrual cycle have widespread prevalence in both PMS and non-PMS sufferers (Metcalf et al., 1990) it seems plausible to expect that they are more likely than emotional changes to be a straightforward function of mechanistic hormonal drive. In fact, the evidence from this thesis so far is contradictory on this point. The folliculogenesis study suggested that physical changes in breast tenderness and bloating over the pill cycle were related to subtle variations in endogenous oestrogen. The reports from PMS patients of cyclical symptoms during extended pill taking from this chapter, however, indicate that both moods and physical symptoms oscillate under constant steroid conditions. The shortcomings of the Clinic data have already been elaborated.

These three hypotheses are tested in the study described in Chapter Six in which a low dose combined monophasic pill was administered in a double-blind, controlled fashion for 25 weeks to volunteers previously well established on a number of different low dose pill formulations. The design of the study is summarized by the schematic diagram in Figure 5.09.

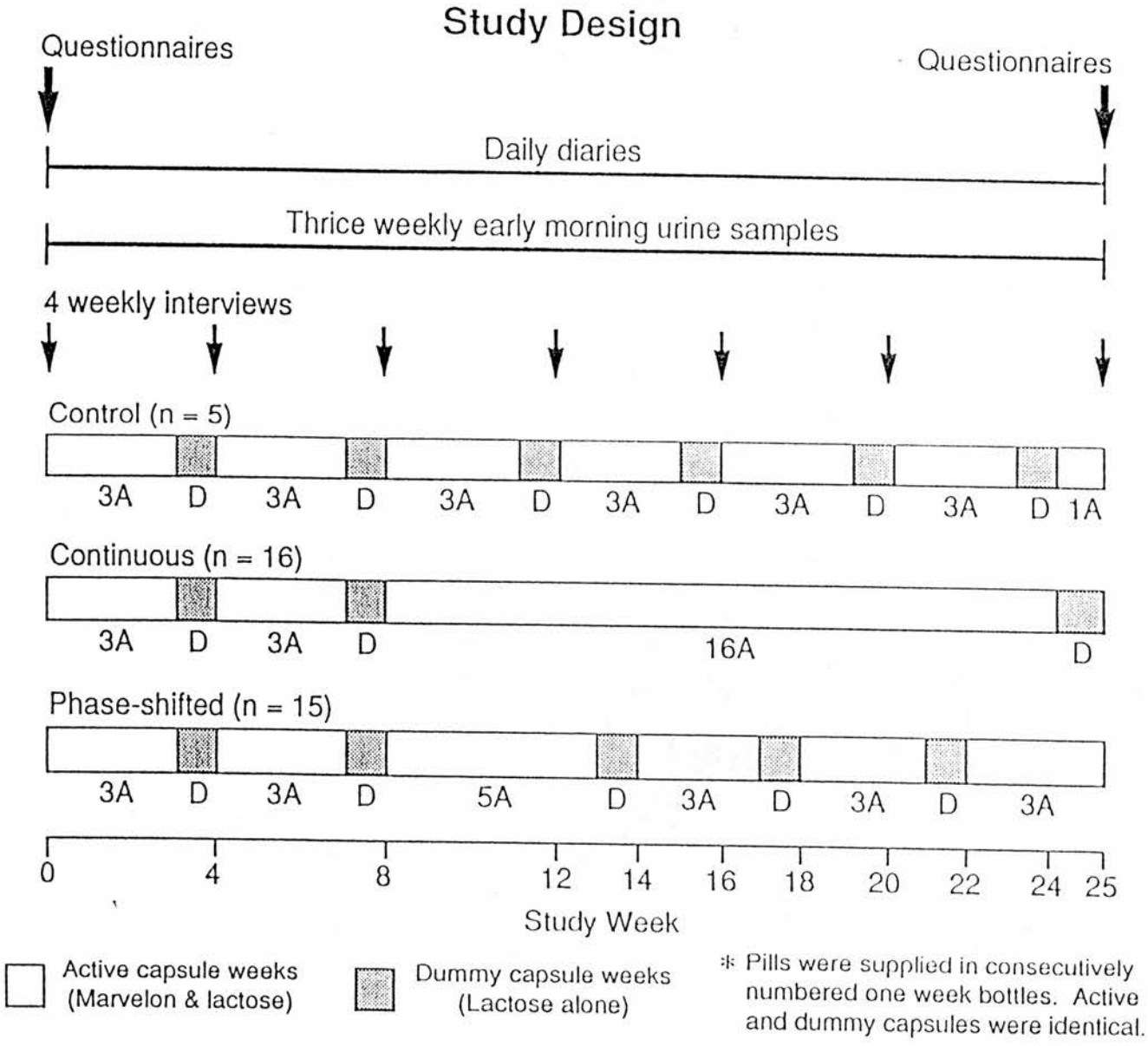

Figure 5.09 Schematic diagram summarizing the design of the double blind, controlled study of pill cycle length manipulation.

Chapter 6 Characterizing an Infradian Rhythm through the Manipulation of Oral Contraceptive Cycle Length: A Double-Blind Controlled Study

6.1 Introduction

This chapter details the findings of a study in which the low dose monophasic OC, Marvelon was taken in three different regimes over more than six months in order to test the hypotheses which were described in the previous chapter. Withdrawal bleeding weeks were built into continuous pill taking using placebos to achieve a double-blind design. The theoretical background to this investigation was considered in detail in Chapter Five.

Ethical approval for all of the methods and procedures employed in this study was obtained prior to its implimentation. Approval was granted in writing by the Paediatric/Reproductive Medicine Ethics of Medical Research sub-committee of the Lothian Health Board on 23rd November, 1989.

6.2 Study Design and Randomization Procedure

6.2.1 The Control Group

A control group was included which underwent conventional four week pill cycles throughout the study. They had a sequence of three weeks of active capsules followed by a week of placebos for six cycles, with active capsules in the 25th and final week of the study. They began a normal packet of Marvelon immediately after finishing the study pill, so the final cycle was therefore 5 weeks long. This group was intended to control for volunteers' expectations of their cycles, and their attribution of changes in well being to the visible occurance of vaginal bleeding. In seeking an endogenous oscillation it was also essential to have a comparison group who remained "entrained" in the usual way. The control group could provide baseline information about the nature, degree, and timing of cyclicity in moods and physical well being over the conventional cycle against which the responses of women undergoing manipulations could be compared.

Another important reason to include a control group was to measure the impact of the study itself on women's assessments of subjective state. In addition to the obvious demands of maintaining daily monitoring for six months, the women in this study had the added stress of double-blindness. While women experiencing menstrual cycles never know for certain when their periods will occur, most women who are well established on OCs know precisely when to expect a bleed. Some women even know at what time of day it is likely to occur. Thus it is rather odd for a woman to be in a situation where she does not know if her cycle will last four weeks or four months. A lack of menstrual bleeding is often a source of anxiety for fear of pregnancy or some physical abnormality. So although the volunteers had consented to undergo manipulated cycles in a blind fashion they might still experience anxiety as a function of the regime.

6.2.2 The Continuous Group

The second group, like the control group, also had two conventional four week cycles at the beginning of the study. This group, which shall be called continuous, went on to have constant active tablet administration for sixteen weeks, followed by a withdrawal bleed in the final study week, 25. They had a conventional 4 week pill cycle immediately after the study. This regime was intended to create freerunning conditions by holding the steroid environment constant thus allowing the hypothesised infradian oscillator to expose itself (H1).

6.2.3 The Phase Shifted Group

The so-called phase shifted group was included to test the second hypothesis (H2) relating to the entraining influence of the steroid cycle on the endogenous mood oscillator. With this model the sytem would be exposed to a transient disruption, and then entrainement returned to its usual pattern. This group also underwent two conventional four week cycles at the start. The third cycle was extended by two weeks of active capsules to create a phase delay equivalent to adding one half of the usual cycle length. After this six week cycle they then returned to conventional cycles for the remainder of the study.

This regime left the group with three weeks of active capsules at the end of the study. They were "due" for a withdrawal bleed, yet they immediately began a packet of

Marvelon and in effect underwent a second phase shift through the consequent seven weeks long cycle. This was longer than the oringinal phase-shift. Although formally the protcol for this study only included 25 weeks of monitoring, most women continued their diary keeping for two to three further weeks. Thus, there are data covering the second phase shift for most women.

For both the phase shifted and continuous groups the first two months served as a baseline. This offered an internal control that would show if a woman tended to experience cyclicty of mood or physical well being during conventional pill use against which the reactions to subsequent manipulations could be compared. Women also had a chance to adjust to the Marvelon if they had switched from another pill formulation. This baseline ought to have ensured that in the final four months of the study when the manipulations actually took place, women's subjective state recording was not clouded by anxiety about the study, by difficulties in adjusting to Marvelon, or by trouble getting used to the diary scales.

6.2.4 Randomization

It was originally intended that sixty women should complete this investigation. This was to be achieved by generating a total of 75 volunteers, and replacing drop-outs from the residual pool of 15. If a woman's own underlying cycle length might be mirrored in her freerunning phase length, then it was desirable to attempt to distribute women with short, intermediate, and long cycles evenly over the three groups. The intention was to take groups of 15 women as they entered the trial and stratify them based on their own central trend, and then randomize them to one of the three groups.

This approach was not possible in practice because of the difficulty in recruiting large numbers. In order to be able to test the experimental hypotheses adequately it was felt that group allocation should be weighted in favour of the two manipulated groups in the following ratio: 12 Controls, 24 Continuous, and 24 Phase shifted. But when it became apparent that recruitment was proceeding slowly and the desired number might not be reached, the distribution was altered so that one-sixth of participants would be in the control group, two-sixths in the phase shifted group, three-sixths in the continuous group.

The numbers were largest in the continuous group to ensure that the primary question under test, whether or not there is an infradian oscillator, could be satisfactorily addressed even if the full number desired was not achieved. It was also anticipated that more women might drop out of the continuous group than the other two because they would be experiencing a much greater disruption to their usual cycle length, and might experience more problems, particularly bleeding abnormalities as a result.

The original randomization blocks of 15 were generated using a random number sequence taken from Fisher & Yates Statistical Tables for Biological, Agricultural and Medical Research (1957). Four blocks and one reserve were generated with three controls, and six phase-shifted and continuous allocations in each. I generated the randomization sequences and passed then to Pamela Warner (PW) who was acting as the blinder. PW randomly allocated a letter to each block from A to E. Group allocations were to be taken from the E group to replace drop-outs.

I became aware of the problem with inadequate numbers early in enrollment, therefore, PW created an algorhythm with which to combine blocks A and B, and blocks C and D into two blocks of thirty and render one control and two phase shifts, continuous. This produced the final 1/6, 2/6, 3/6 distribution. Had sixty women completed the study there would have been ten controls, twenty phase shifted, and thirty continuous. It proved to be impractical to stratify women based on central trend in cycle length, and this procedure was abandoned. In fact, many women had difficulty recalling their usual cycle length with any accuracy, possibly due to prolonged pill use in some cases, and therefore such a stratification device would probably have been of limited usefulness.

6.3 Recruitment Procedures and Selection Criteria

A number of different recruitment procedures were used to interest volunteers in the study. Ultimately the number of women that took part was about two thirds of the projected number. All of the of the volunteers for this study were recruited from amongst women attending the Lothian Health Board Family Planning Centre (FPC) at Dean Terrace, Edinburgh. Three separate recruitment drives were carried out. Those women who volunteered to take part in the study were expected to meet the following inclusion criteria.

6.3.1 Inclusion Criteria for Volunteers

1) Age between 20 and 40 years, or 35 if a smoker. Twenty was taken as a lower age limit for the same reason as in the folliculogenesis study, to try and ensure gynaecological maturity. Younger women are also more likely to be living at home, with parents who may not know that they are using contraception or are in a sexual relationship. The regular telephone and postal contact required in a prospective study make it difficult to conceal participation form other members of the household, which may cause difficulties. Older women may also be better equiped to deal with the heavy demands of long term diary keeping and urine collection. The upper age limits were chosen to reflect the current wisdom about age/smoking related risk and pill use. We exploited the fact that the FPC doctors had already made an assessment of the woman's age and smoking related risk for combined pill use to avoid the need to make an additional assessment.

2) Nulliparity or low parity. Repeated pregnancies may effect cycle length, bleeding experience, or the response to exogenous steroids (eg. Treloar et al., 1967, Anderson, 1989). They may also influence the hypothesized infradian mood rhythm. Differences in parity simply add another source of variance, which we felt was best excluded. In practice the majority of women who attend the FPC are of low parity, so this criterion did not alter the recruitment pool.

3) No manipulation of her pill cycle in the last calendar year. Clearly, it was desirable only to accept women into the study who were "entrained" to a similar degree by the conventional 28 day pill cycle in a study designed to test the existence of an infradian rhythm. This might help to control another, large source of inter-individual variance.

4) Use of the present combined oral contraceptive formulation for at least three cycles. Women needed to be moderately well established on their current pill formulation, and not taking a progesterone only preparation. This way if they did have to switch from another formulation to the study pill the effects would be minimized.

5) No contraindication to the use of combined oral contraception in general, and no past history of mallignancy, serious metabolic, haematological, liver, or renal disease. These are absolute contraindications to OC use. It is unlikely that any woman with

these risk factors would be attending the FPC taking the pill, nevertheless, the possibility was discounted based on the Clinic notes and initial interviews

6) No intention to start a pregnancy within three months of completing the study. Some disruption to cycle length and bleeding patterns might be expected to occur after completion of the study given its nature. For example, were extended pill taking to cause any degree of endometrial hyper- or hypoplasia, it might be best for a woman to experience several pill-free cycles before trying to conceive to permit the endometrium to repair itself fully.

7) Living within five miles of Edinburgh, or able to come into the city for sample collections and interviews. All meetings were scheduled to take place in the centre of town, and volunteers were reimbursed their travel expenses.

8) Report of some degree of cyclical physical or mood experience over the pill cycle. Obviously, it was desirable for women to show a degree of cyclicity, otherwise detecting an infradian oscillator becomes an irrelevance. In practice, some of the women ultimately enrolled did not report significant cyclical change, but the difficulty in recruiting adequate numbers for the study militated against excluding them.

6.3.2 First Recruitment Drive

The MHRAQ-2 which was used as the main recruitment device for this study was described in Chapter Four. The final page of MHRAQ-2 briefly outlined the nature of the cycle manipulation study and invited women who were taking the pill to provide their name, address, and telephone number if they wished to be contacted with further information. (See Appendix 4.02) This self-administered questionnaire was a good tool for conveying information and arousing interest that might encourage women to take part in further research without "putting them on the spot" with a face-to-face request to join a study. Those women who did not wish to take part simply left this page of the questionnaire blank. This technique had the further advantage that those women who did volunteer were probably highly motivated. It was noted there how the questionnaire sample of women may over-represent certain sub-groups of the general population. Nevertheless, it is probably one of the best places from which to recruit established OC users given the very high prescription rate in the Clinic[1].

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Twenty-two per cent (22%, n=151) of the almost 700 women who completed the questionnaire gave their name and address to be contacted. Twenty-five of the 151 were deemed not to fulfill the selection criteria on the basis of their questionnaire responses. They were either too old, too young, or not currently using the pill. Permission was granted by Dr. Elizabeth Barden, then acting director of the FPC, to inspect the Clinic notes of those women expressing interest in the study to assess their eligibility. A further twenty-three women were considered unsuitable because they were using a progesterone-only pill due to contraindications for the combined pill such as high blood pressure or migraine, or because they had had a previous adverse reaction to Marvelon.

After the clinic notes had been examined for contraindications the remaining women offering their names were contacted by telephone, or by letter if they had not provided a phone number (See Appendix 6.01). The aim of the study was loosely described as "a study of how women feel when they are using oral contraceptives". At the time of telephone contact, it was first ensured that a woman met the slection criteria, and then more precise details were offered about the nature of the investigation and the demands that would be made on her time (diaries, urines, etc.). Women were told that the study concerned finding out how cycle length relates to well being. Women were reassured over the phone that the alterations that would be made in their pill cycle would not be harmful in any way, and that there was no greater risk of pregnancy than when using the pill normally.

Of the remaining 103, seventeen proved uncontactable as they did not provide a phone number and did not respond to letters. A further fifty-four women did not respond to repeated telephone calls and messages, or declined to take part at the first telephone contact. Women gave a number of reasons for not wishing to take part, few of which were medical. Most reasons were social and revealed a lack of understanding of the pill's mode of action, and a great deal of fear surrounding the risks associated with pill use. The list below includes reasons women gave for not wishing to take part.

* "I can't be bothered with it"- apathy, a feeling that it would involve too much effort

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One reason why such a large proportion of women at the FPC are pill takers may be that pill takers specifically attend Dean Terrace because they know that they will have their pills prescribed, and dispensed to them on the spot. The large number of evening clinics also make it convenient for working women.

* Fears and unwillingness expressed by partner.
* Fear of side effects or the risk of pregnancy.
* Unhappy that she would not know when bleeds would occur, "changing my routine".
* "I don't want to muck about with my hormones"- fear of the unfamiliar, 'experimental' nature of the study.
* Not willing to switch pill types, settled on current pill and had difficulties with other formulations.
* Under a great deal of stress at home or at work.
* Relationship difficulties, break-up.
* Lack of time.
* Lack of transport or too great a distance to travel.
* About to get married.
* Planning to come off the pill.
* Planning a pregnancy.
* Having other hormonal treatment.
* Menstrual migraine or withdrawal headaches.

Ultimately only thirty (30) of the original one hundred and fifty-one women actually volunteered to enroll in the study, which is less than 20% and well below the desired number of participants. Other steps were taken to recruit more women.

6.3.3 Second Recruitment Drive

The second recruitment drive took the form of a poster placed in the waiting room at the FPC during July 1990. The text of the poster is contained in Appendix 6.02. This poster did not generate any interest at all, and no one left her name or tried to contact me during the approximately four weeks in June and July that it was in place. We had originally thought that a poster would make it easier for women to express their interest, and offer a better tool for pre-selection of appropriate volunteers, but this proved not to be the case.

The poster seemed to lack an important element present in the questionnaire. Namely, the questionnaire awakened thought and comment about novel or previously silent subjects like attitudes to vaginal bleeding. In accustoming women to the idea of such questions it perhaps went some way to persuading them that they personnally could

play an active part in investigations designed to answer those questions. Some support for this theory is offered by the nature of the comments women made on the first questionnaire: comments applauding research efforts in this area.

6.3.4 Third Recruitment Drive

I decided to re-issue the original MHRAQ-2 with modifications so that it was quicker to complete, and was specifically directed at women using the pill. The result was MHRAQ-3. It contained 31 questions, some requiring multiple responses to Likert-type scales, in one, four-page questionnaire derived from the first part of MHRAQ-2 (See Appendix 6.03). The procedure for administration was also simplified. Stacks of questionnaires, pens, clipboards, and freepost envelopes were left in the FPC waiting room under a sign that read: *"If you are on the pill would you please fill in one of the questionnaires below."* This was done primarily because the staff at reception were not happy about asking women if they were taking the pill or not, as they felt it breached their confidentiality. This also made it easier for those women who did not wish to fill in a questionnaire to avoid doing so, again preferentially selecting those women who were more highly motivated.

One hundred and fifty-seven (157) modified questionnaires were filled-in over the course of nine weeks from August to October, 1990. Sixty-four women (64), or over 40% expressed a willingness to be contacted. Fifteen (15) of these were unsuitable based on their questionnaire responses. Thirty-two (32) declined to take part at the first telephone contact for the same sorts of reasons outlined above. The remaining 17 were enrolled in the study, representing 11% of all respondants and 26% of those who had specifically expressed interest.

6.3.5 Summary of Recruitment Efforts for Cycle Manipulation Study

It took approximately one calendar year to recruit and enroll the volunteers for this study. During this time approximately 1175 women were asked to take part. Of this number 47 (4%) enrolled in the study and 36 (3%) completed it. I believe that there were three primary factors contributing to the low response rate. 1) The concept of systematically altering the length of one's cycle and not knowing when bleeds are going to occur is seen as threatening and alien to many women. 2) The study was to be quite

demanding, requiring consistant daily inputs over six months. 3) There was a long and unforeseen delay between the administration of the first questionnaire and initial contacts with women due to difficulties in securing a supply of oral contraceptives and matched placebos for the study.

6.4 Methods

This study was conducted in a similar manner to the folliculogenesis investigation using daily diaries prospectively to obtain information about subjective state, while at the same time monitoring steroid levels with urinary hormone tracking. Equally demographic details were gathered at the time of enrollment and volunteers were required to complete a number of psychometric tests. The protocol was designed to last for 25 weeks, but in practice many women continued monitoring for as much as seven months. Full descriptions of the pill formulation, design, interview instruments, and prospective monitoring procedures are contained in the sections that follow.

6.4.1 Pill Formulation and Presentation

6.4.1.1 The pursuit of double-blindness

There is a good deal of evidence that women have expectations about their menstrual or pill cycles, and that sensations and changes may be wrongly or stereotypically attributed to the events of the cycle (eg. Bains & Slade, 1988; Ruble, 1977; Parlee, 1974). In order to minimize these effects, and to ensure that knowledge of group allocation did not bias the researcher in the conduct of the study, all efforts were made to achieve a double-blind design. The intention of the original study design was to use one of the new-generation gestagen containing monophasic pills (Femodene, Minulet, or Marvelon) for which matched placebo tablets had been obtained, and generate continuous strip-packs of pills with withdrawal bleeding weeks built in at the desired intervals.

Achieving this proved to be a substantial obstacle to the rapid implementation of this study. The three major pharmaceutical manufacturers who produce monophasic pills of this type were approached, namely- Schering Health Care Limited (Femodene), Wyeth Laboratories (Minulet), and Organon International (Marvelon). It was theoretically possible for any of these firms to produce the special matched placebo pills required, but there were two insurmountable problems: one practical and economic and the other

ethico-legal. In order to make matched placebos the machines that are normally devoted to the manufacture of pills would have to be stopped, the active ingedients removed and set going again with an adjusted 'dose' of filler on its own. Under normal circumstances these machines produce over one hundred thousand active tablets a minute. But only about two thousand placebos were required for this trial. An interuption to the manufacturing process of many minutes, even hours, to make a small number of placebos would have cost the drug company a considerable sum in lost profits. Special strip packaging would apparently have proved even more costly and difficult.

The second difficulty was that it is illegal in Britain to produce a drug preparation which looks exactly like a marketed product, but does not contain the active ingredient. This is even the case for matched placebos in clinical trials. The reason for this is to protect against the risk, however remote, that someone might take the placebo believing it were the active, and suffer whatever medical consequences as a result (in this case, of course, pregnancy). Therefore, it appeared that to achieve double-blindness with an oral contraceptive one would have to specially produce not only the placebos, but the actives as well. OCs are generally very small and unusual shapes, and the tooling equipment to make, for example, a 6mm, white, bi-convex, sugar coated tablet is not readily available outside the drug companies that make pills.

The option of an open study without matched placebos, but in which packaging was used to obscure cycle phase, was considered. Possibilities were explored with pharmacy departments in Edinburgh, Glasgow, and London to package active tablets and unmatched placebos in opaque weekly bottles so that volunteers would only know at the beginning of a given week if they would be having a withdrawal bleed. Ultimately double-blindness was achieved. Prof. J. M. Newton at the School of Pharmacy of the University of London proposed that active pills be packed inside opaque gelatine capsules surrounded by lactose powder as filler. Placebos could then be created using capsules packed with lactose powder alone.

6.4.1.2 Formulation, encapsulation, packaging and labelling

In the end the monophasic pill, Marvelon, was provided for the trial by Organon UK. Marvelon contains 30µg of Ethinyl Estradiol (EE) and 150µg of the third generation gestagen, Desogestrel (DSG), and is manufactured in Holland by Organon International. Organon kindly agreed to supply ten thousand (10,000) ordinary,

unpackaged Marvelon tablets for the study. These were sent to St. Bartholomew's Hospital, London where the encapsulation took place.

Prof. Newton organised for the Marvelon tablets to be packed in lactose powder in size 0, opaque, white, gelatine capsules. The work was carried out by a registered pharmacist, under the supervision of Prof. Newton and Dr Michael Lillywhite of St. Bartholomew's Hospital. The precise protocol for encapsulation, and reconciliation and checking is described in Appendix 6.04 in a statement supplied by John Young, Bart's Production Pharmacist. An assessment was made of whether or not it would be necessary to enclose an unmarked, 6mm, white, biconvex, placebo tablet in the placebo capsules. The pharmacy determined that the placebo capsules looked and felt sufficiently similar to encapsulated actives to use lactose powder alone in the placebos.

Bottles which contained either seven days' supply of Marvelon or placebo sported two labels: a peelable content label and a study label. I placed the bottles in appropriate 25 week sequences according to the three regimes described above. The content label was peeled off and placed on a reconcillition sheet, while the study label and bottle lid were marked with the study week number. Pam Warner then acted as "blinder". She added the volunteer code number to the prepared study labels according to the random-number generated, master list for group allocation.

A Department of Health Doctors and Dentists exemption certificate was obtained to permit the use Marvelon in this altered presentation, and in the manner outlined above. Any deviation from the strict prescription guidelines laid down in the datasheet for this pill requires that exemption be obtained. We were advised by Organon U.K. that the lactose would delay pill absorption by approximately one hour. This would be equivalent to injesting the pill just after eating a bar of chocolate or drinking a glass of milk (David Hollingworth, 1990, personnal communication). Study participants were advised of this and requested to take their study capsules one hour earlier than usual.

Individuals were switched to Marvelon, if they were not already taking it, from their existing low dose combined formulation after a seven day pfi (i.e. capsules begun on the eighth pill free day). Women who were already using Marvelon began the study pills after a seven day pill free interval as always. I was assured by the Ex-Director of Family Planning and Well Woman Services for Lothian Region, Dr. Nancy Loudon, that there was no need to have a shorter pfi, or take extra precautions when switching

pill formulations unless a woman was changing from a higher to a lower dose of oestrogen (Nancy Loudon, 1989, personnal communication).

At the end of the twenty-five weeks of encapsulated tablet taking, volunteers were given an ordinary packet of Marvelon in a sealed envelope and instructed to begin taking the enclosed pills the day after they finished the last bottled capsule. The regular strip packs of Marvelon were also generously provided by Organon U.K.. This procedure was followed because all the participants in this study were using the pill for contraception (see section 6.2 above).

6.4.2 Prospective Monitoring of Hormones and Subjective State

The women taking part in this study were required to complete a daily form diary rating mood and physical well being. They were also requested to collect an early morning urine sample three times a week at approximately even intervals. If a woman did not wish to, or was unable to make the urine collection, she was not excluded from the study.

6.4.2.1 Ordinal scale daily diary

In this study a 16-item ordinal scale diary form was used. It was intermediate between the visual analogue diary described in Chapter Three and the PMS Clinic instument described in Chapter Five (See Appendix 6.05).

Visual analogue scales (VAS) were abandoned in this study for three reasons. First of all, it was apparent from the folliculogenesis study that some women found the concept of a scale that assesses ones own internal state from best ever to worst ever difficult to understand. Secondly, VAS's should be transformed by the range which a woman used before they can be compared across women. Even if the scale is adjusted to take account of the way the woman filled it in, it is impossible to know whether or not her variance is comparable to that of another woman, or whether some women simply experience less variation in their well being. The third drawback is a practical one. VAS must be coded prior to data entry which is very time-consuming if they are used in large numbers. Given that the current study monitored twice as many women for two and a half times as long as the first study, the use of VAS's was prohibited by time constraints.

Ordinal scales have the advantage over VAS's that they can be compared across women when the extremes are pre-defined. Because it was felt that the nought to five scale of the Clinic diary did not allow a broad or subtle enough range, this scale ran from zero to ten. "Not at all" was printed over the zero, "moderate" above five, and "extreme" over ten. The ordinal scale diary seemed more intelligible to the volunteers, and was easier to score than the VAS.

This diary contained fewer scales than the VAS diary. The questions about day length, caffeine intake and smoking were all removed. A number of scales were removed based on the factor analysis of VAS diary results from Chapter Three to eliminate repitition. Three variables were dropped from PC1: "creative" because it seemed to hold limited meaning for women, and was generally scored very low, and "relaxed" and "getting on well with others" because they seemed to be highly correlated with the "feeling good about youself" and "cheerful and happy" scales. Equally "mood up and down" and "lacking self control" were removed, as negative affect was adequately covered by "depressed and unhappy", "irritable", "aggressive / angry", and "tense and anxious". "Feeling sexually attractive" was removed as it was very highly correlated with "sexual interest" and "sexual activity".

One scale was added to this diary which was not included in the VAS diary: "headache". I felt it was important to include this scale in a study which invovled prolonging pill cycle length in order to see if it would increase the frequency or severity of headaches, as there is evidence that headaches tend to cluster around the time of vaginal bleeding (Dalton, 1983). Another factor which this study was particularly concerned to monitor was vaginal bleeding experience. Therefore, a statement requesting women to qualify the type of bleeding they experienced was included. It was hoped that by asking women whether or not they believed they were experiencing a period or spotting, one might be able to assess the significance that they were attaching to concurrent moods and physical sensations. Like both other diaries, this one contained two blank scales for women to monitor any additional symptom which was meaningful to them.

As with both previous diaries, volunteers were instructed to complete one form last thing each night, and to relate their ratings to the feelings that they had experienced over the previous 24 hours. The daily diary instruction sheet is contained in Appendix 6.06. Because of the sheer volume of daily diaries to be generated by this investigation (about

10,000) their presentation was changed from the usual 7-day booklet. Twenty-eight diaries were fixed together in A5 size booklets, printed on both sides of the page. Strictly speaking volunteers should be prevented from retaining large numbers of contiguous daily ratings to prevent them looking back at their scores as this may alter subsequent scoring (Gift, 1989). However, it was felt that monthly booklets would make administation easier, and volunteers were urged not to go back through their previous ratings. Again, to spare expense and undue complexity the order of the scales did not vary from day to day. Ideally the order of scales should vary to prevent response sets (Gift, 1989). Some women who appeared to become bored with the scales around mid-study were encouraged to fill the form in from bottom to top, or vary the order in which they considered the scales.

6.4.2.2 Hormonal assessments

Given the extremely low levels of urinary progesterone found in low dose pill takers in the folliculogenesis study, only oestrone-3-glucuronide was measured in all samples in this investigation. In a few women who showed oestrone levels within the ovulatory range "spot" pregnanediol levels were assessed to determine if ovulation might have occurred. One urine sample per month was entered for a pregnancy test as a way of reassuring women that they were not pregnant in the absence of monthly withdrawal bleeds.

Oestrone was tracked in urine in the same manner as described in Chapter Three, except that samples were collected three times a week rather than daily. The oestrone ELISA's for this study were preformed in the MRC Reproductive Biology Unit by Irene Cooper and Gillian Sutherland. The protocol for the assay was altered slightly to improve its performance. It was determined that the assay was unable to come to equilibrium binding in a one hour incubation, and that use of this short incubation time was increasing the variablity of sample replicates. Therefore, the incubation was changed to overnight at 4° C. The dilution of the reagents was adjusted to take account of this change. The antibody was made up to a 1 in 100,000 dilution in assay buffer, and the label to a 1 in 10,000 dilution. This change in protocol also allowed a larger number of samples to be included in each assay without jepordizing the accuracy of the readings.

The inter- and intra-assay coefficients of variation (C.V.) were calculated from the quality controls of 16 assays. They were as follows: between assay C.V.- low QC 20.2% (8.2 ng/ml) , medium QC 11.9% (16.5 ng/ml), high QC 9.4% (51.2 ng/ml);

within assay C.V.- low QC 10.2%, medium QC 5.5%, high 5.9%. This calculation includes drift from the middle of the first plate to the end of the second in a two plate assay. These C.V.'s compare favourably with the previous performance of the assay used at a one hour incubation.

If an individual's oestrone profile showed values steadily increasing over a withdrawal bleeding interval and into active pill taking at levels that would indicate peri-ovulation in a normal menstrual cycle then ovulation was supected. In the normal menstrual cycle the peak level of progesterone is normally obtained approximately eight days after oestrogen peaks. With no prior information about endogenous progesterone dynamics in an ovulatory pill cycle, I used the menstrual cycle as a guide. If ovulation has occured pregnanediol levels should be elevated for the remainder of the cycle above about 0.5µmol/mmol.

Thus the urine sample that was nearest to eight days after the peak measured level of oestrone was entered into a pregnanediol ELISA for each cycle in which a woman showed evelated oestrogen. Assays were preformed by the staff of the NHS Reproductive Endocrinology Laboratories (REL) at the Centre for Reproductive Biology. This is the routine ELISA assay and is preformed according to the same protocol outlined in Chapter Three.

One urine sample each month was also submitted for a pregnancy test which was assayed for the presence of human chorionic gonadotrophin (ßhCG) by REL. A common source of anxiety and dissatisfaction in the "tricycle study" participants (Loudon, et. al., 1977) was the lack of a regular monthly bleed to reassure them that they were not pregnant. While the chance of conception was quite remote, I wished to ensure that an individual's prospective daily diary ratings were not clouded by a repeated or a chronic anxiety that she might be pregnant because she was not bleeding every fourth week. The assay is sensitive enough to detect pregnancy two weeks after conception, therefore, regular testing acted as a safeguard that a pregnancy would be detected in very early gestation.

6.4.3 Enrollment Interview

Volunteers were enrolled in the study during a pill free interval a few days before they were due to begin a new packet of pills. Every woman came to an interview scheduled

to last for approximately one hour in the Research Ward (54) of the Royal Infirmary of Edinburgh. Enrollment took place in two groups because of the two waves of recruitment. The first two-thirds of participants entered the study between June and August 1990, and the final third between October and December 1990. All volunteers had completed the study by eary May, 1991. At the time of enrollment each volunteer was given a comprehensive information sheet to read. A copy can be found in Appendix 6.06.

6.4.3.1 Informed consent

After reading the information sheet, the volunteer provided informed consent in writing on a consent form and offered her G.P.'s address so that s/he could be informed of her patient's participation (see Appendices 6.07 and 6.08 for consent form and G.P.'s letter). She was then taken through the interview schedule contained in the Appendix (6.09) and was requested to complete a number of psychometric tests.

6.4.3.2 Interview schedule

The interview schedule obtained information about age, smoking, parity, pill taking history, PMS status, a retrospective summary of cyclical experience, pill effects on cycle experience, usual menstrual cycle length, pregnancy and post-partum experience, and recent life events and psychiatric history. All of these factors were thought to be of potential relevance to the manner in which women would experience this investigation. The chart for recording retrospective cyclical experience is based loosely on the retrospective PMS assessment contained in MHRAQ-1. The questions on life events are derived from previous interview schedules used in research studies by John Bancroft's group (see for example Walker, 1987). Pill, menstrual cycle, and PMS history all may have obvious relevance to a study of this kind. Recent adverse life events, psychiatric history, and experience of low mood after pregnancy are important as they might be predictive of negative reactions to the study, or of a high background level of stress which would make it difficult to interpret an individual's prospective ratings.

6.4.3.3 Psychometric tests

Three different self-administered psychometric tests were used to assess parameters that might be prognostic of women's reactions to manipulation of their cycle length. Copies of these are contained in Appendices 6.10 to 6.12. The Eysenck Personality Inventory

(EPI) Form B was used to assess personality. (See discussion of EPI, Form A in Chapter Three).

Current clinical depression was screened for using the Beck Depression Inventory (BDI). If a woman was severely depressed when she entered the study then daily diary ratings would probably be invalid, and therefore she ought to be excluded. The degree of subclinical depression might relate to the way in which a woman scored diary scales reflecting negative affect, both around the time of bleeds and during other cycle phases. A review of the research uses of the Beck Depression Inventory (BDI) over the last 25 years has recently been made (Beck, Steer, & Garbin, 1988). Although the Beck was originally devised for use with psychiatric patients, it has been widely used in non-psychiatric populations.

Finally, Locus of Control as it relates to health was measured by the Multidimensional Health Locus of Control Scale (MHLCS), developed by Wallston, Wallston & DeVellis, 1978. This scale measures three constructs of locus of control. The first, Internal Health Locus of Control, is a measure of how strongly an individual feels she is in control of her own health status. The other two parameters are different aspects of external locus of control, or to what extent one believes ones health is controlled by external forces. The Powerful Others dimension relates to the influence of doctors, nurses, family members, etc., while the Chance dimension measures the extent to which one believes one's health is fated.

I hypothesized that those women who were more externally controlled would be more willing to tolerate manipulations of their cycle, because they would accept the control of the researcher over their experience (as a powerful other), or would simply attribute the experience to "the luck of the draw". Internally controlled women, on the other hand, would be frustrated by not knowing when their bleeds were scheduled to occur. They might report more adverse effects or dissatisfaction with the study as they were not able to control their health experience as they normally do. Severity of women's cycle-related symptoms has been associated with locus of control using this instrument (Harding, 1987), and external LOC has been shown to rise premenstrually in women with prospectively confirmed PMS (O'Boyle, Severino & Hurt, 1988).

After completing the interview schedule and psychometric tests, volunteers were instructed in the method of completing daily diaries and collecting urine samples

(described in Instruction sheet, Appendix 6.06). They were given a five week supply of capsules at this time, and instructed to begin pill taking on the usual day that they would begin a new packet.

6.4.4 Volunteer Monitoring and Case Notes

Approximately every four weeks volunteers returned to the Royal Infirmary for brief meetings. These were devised to keep a careful check on how women were feeling, and as an important way of maintaining motivation over the six to seven months that each woman kept up monitoring. Diaries and samples were collected at this time, and new supplies provided to last until the time of the next meeting. At every visit a woman was asked "how she had been getting on since the last visit?". These meetings offered a form of monthly retrospective in which volunteers could assess how they felt the study was effecting them- its demands, the formulation, or the cycle manipulations. They could also raise issues in their lives that were influencing thier feelings, and diary ratings. The case notes provided quite a lot of information about women's perceptions of the manipulations they were undergoing, and offer anecdotal information not contained in the diary.

6.4.5 Final Structured Interview

Once a woman had completed all 25 weeks of the study, and had begun to take the ordinary packet of Marvelon, she was scheduled for an hour long final interview. A copy of the final interview schedule is contained in the Appendix (6.13). The volunteer was asked a number of questions pertaining to how positively she had viewed the experience, what changes she had noticed in her physical and emotional well being while taking part, how her actual experience related to her prior expectations, any dislikes, thoughts about irregular bleeding and fear of pregnancy. Her comments were written down in summary, or verbatim if of particular relevance to the study objectives. After this discussion, she was asked to complete a written assessment of her experience which particularly concentrated on cyclical symptoms and potential side effects (see Appendix 6.14). After this was completed and discussed, her group allocation was revealled.

6.4.6 Methods Used to Analyse Prospective Ratings

This investigation approached novel hypotheses in a novel manner. It was not clear how the analysis of prospective measures should be carried out. The features of the rhythm, if present, were not yet know, and it was part of the objective of the study to describe those features. Therefore, when the protocol was originally developed it was planned to carry out a descriptive analysis on a single case basis. However, a number of more sophistocated analytic techniques were considered.

6.4.6.1 Mathematical techniques of rhythm analysis

Minors & Waterhouse (1989) provide a very useful summary of the available techniques of analysis for biological rhythm data and the constraints placed on their use. They begin by acknowledging the complexity of the problem, and the fact that most techniques were developed for use with data from "physical systems" in fields like engineering or physics, or for economic forecasting "where numerous cycles of periodic phenomena are frequently available with a high rate of equidistant sampling" (p.272). The rigid conditions for their use are almost never met with biological data, which is inherently variable, vulnerable to a variety of internal and external influences, and difficult to collect over a protracted timespan.

Frequent equidistant sampling has been carried out in this study. Minors & Waterhouse (1989) recommend that if nothing is known about a rhythm, samples be made at least six times during its anticipated period. They note that if sampling frequency is too high measures will not be independent, which influences the utility and validity of some statistical techniques. It is very likely that sucessive daily ratings of well being are not indepentent of one another. However, it remains important to have daily data because well being is not likely to show an even profile over time; indeed, if it constitutes the sort of 'relaxation oscillator' proposed earlier it is vital to have frequent measurements in order to best characterize its features over time. Nevertheless, frequently sampled biological time series data will contain noise that may obscure the biologically meaningful aspects of the rhythm, and smoothing is generally required.

One potential method is ANOVA. ANOVA can be used to detect whether or not there is significant variation between several time points in a biological time series, and with data of known period, any length of oscillation can be analysed (Minors & Waterhouse,

1989). But this technique does not give any information about the characteristics of a rhythm, nor can it detect a rhythm if the period is unknown, as it is in this case

Time Series Analysis (TSA) is also often used to analyse rhythm data. Cosinor-rhythmometry was first described by Halberg et al. in 1972 and invovles fitting a cosine function to the rhythm in question (Minors & Waterhouse, 1989). But this technique requires that the period be known or can be assumed *a priori*. It also assumes that the rhythm can be approximated by a cosine curve, and that the residual errors are independent, and normally distributed. Cosinor is also not able to cope with changes in rhythm parameters with time. So for example, it would not be appropriate to use with the continuous group's diary data if cyclicity damps out over time due to weak endogenicity and/or lack of reinforcement from the primary zeitgeber/dominant oscillator (cycling steroid hormones).

There are ways to use cosinor analysis if one assumes the period of an unknown rhythm. More complex, but still essentially sinusoidal oscillations can be described by elaborations of cosinor in which harmonics are added to a basic cosine curve. This involves Fourier's theorem for spectral analysis which says that any waveform can be reproduced by a combination of sine and cosine terms (Minors & Waterhouse, 1989). The risk is that biologically meaningless noise will be included along with the fundamental rhythm. One can fit a curve to any time series dataset- even if it has been generated randomly- using a sufficiently complex function, but it will be meaningless. Several computer packages exist to perform such analyses but they were either unavailable, or inappropriate for use in this thesis[2].

A third technique is autocorrelation. Autocorrelation invovles correlating the time series in question with a duplicate of itself after the introduction of various time lags. If there is a rhythm present it will be revealled by a high correlation between duplicated segments of the time series after the appropriate shift in phase. More simply stated it is a means of seeing if sections of a time series overlap, or repeat themselves. It is unlikely that a long string of sequential values will precisely repeat their form by chance alone. This technique, like the others has drawbacks. The data need to be "stationary"

2

For example, in 1990 Teicher & Barber described an easy-to-use package written for Macintosh computers which is specifically designed to deal with biological rhythm data, and performs "multioscillator cosinor analysis" on rhythms of known or unknown period. It seemed that this programme would be ideal to analyse this dataset, but it was unfortunately unobtainable.

with no tendency for the amplitude, period, etc. of the rhythm to change over time, and one must have data for at least four cycles of the period which is being sought (Minors & Waterhouse, 1989). As described above for cosinor analysis, there is no reason to assume in this investigation that the data will meet these constraints. For example, in the continuous group four months may be insufficient time to observe four repetitions of the infradian rhythm if the free running period is 35 to 40 days.

After considering these matematical techniques to detect and describe the hypothesized rhythm I returned to the simplest method: plotting the data over time, "eyeballing" it, and describing its features within and across individuals. Minors & Waterhouse (1989) summarize the utility of descriptive techniques:

> "[A] description of the raw data will remain an important part of rhythm analysis.... Even though it may not be possible to quantify the rhythm mathematically, it may be sufficient to show that the form of the rhythm is reproducible in many individuals or may be changed in a reproducible way with some (fixed) experimental manipulation." (p.291)

Sollberger (1965) provides a good synopsis of the relationship of biological rhythm research to statistical proof:

> "In the earlier days of biological rhythm research, it was important to convince the sceptics that rhythms really exist, and statistics was the way to do it....[T]his achieved more convincing than proving. Fortunately, the rhythms have become accepted and the real proofs have been obtained by the simplest statistical method possible, *sheer repetition* (my emphasis). This is actually an effective test. If we have only three or four individuals, congruent curves are proof enough since it would require quite a lot of chance to arrange all the values in the correct timing and sequences, if they were really random." (p.20)

Thus, after an inspection of the distribution of daily diary ratings over time, judgements were made about both the presence of a rhythm and the clinical relevance of specific women's experience over the course of the study. Individuals were dealt with on a single-case basis in the first instance, and then similar patterns of experience were grouped where appropriate. For example, individuals may be grouped if they have been subjected to the same environmental circumstances and the same entraining influences or zeitgebers, as they were in the phase shifted group.

6.4.6.2 Data Reduction and Smoothing

The results of the descriptive analyses are detailed in the sections below. Certain variables were isolated for close inspection, and the noise in the data was reduced to improve the clarity of longitudinal profiles and to aid interpretation. For every woman in each group Student t-tests were used to make a gross asessment of the change in severity of symptoms over time by comparing the mean diary ratings for each symptom during the first eight weeks (baseline) of the study with the mean for the subsequent 17 weeks (manipulation). These means were derived from the raw daily data. Selected variables for each individual were also plotted. The data were examined for evidence of a regular oscillation over time and trends across women in the three groups.

In order to reduce the amount of noise in biological time series data it is usual to smooth it in some way. Normally one relates a given measurement to the points that surround it using a moving average, which may be unweighted or weighted to emphasize the point in question. This technique will systematically reduce the number of data points, and allow general trends to emerge from background noise. It can, however, produce spurious oscillations if adjacent or nearly adjacent points are fluctuating randomly in the same direction. (Sollberger, 1965; Minors & Waterhouse, 1989). Instead of using a moving average with this data set, the data was condensed by dividing it up into discontinuous 4-day phases. The reason that four day blocks were taken is because the conventional 28 day pill cycle can be divided evenly into seven blocks of four days. A 4-day block is large enough to incorporate the odd missed day of ratings, yet small enough not to obscure rapid variations in the data which may occur from one day to the next. Four-day phases are also consistent with the previous methods used in this thesis.

It was clear that certain diary variables were highly intercorrelated. This is to be expected when multiple scales are measuring features of the same thing, for example, negative affect. Some women may distinguish little between such features, while others may interpret these scales to be quite discrete emotions. On inspection of individual's data it became evident that "cheerful and happy", "feeling good about self", and "energetic and active" co-vary to a large extent; as do "irritable", "aggressive and angry", "tense and anxious", and "depressed and unhappy". Furthermore, there seemed to be a particularly close association between "irritable" and "aggressive and angry", and between "tense and anxious" and "depressed and unhappy". These were

interpreted as two distinct components of negative affect: an active, outwardly directed component on one hand, and a passive, inwardly directed component on the other.

Positive affect seemed to show little predictable oscillation in the raw data. While changes in happiness, energy, etc. are undoubtably neglected covariates of the steroid cycle (eg. Stewart, 1989; Asso, 1991), it is the cyclical negative changes which women tend to emphasize. Therefore the two components of negative affect described above, and the most commonly reported physical symptoms were isolated for analysis. The six variables were: 1) either "irritable" or "aggressive and angry", 2) either "tense and anxious" or "depressed and unhappy", 3) breast tenderness, 4) bloating, 5) period type pain, and 6) bleeding. Irritability and depression are two of the most frequently discussed cyclical symptoms in the PMS literature. But as they correlated strongly with other scales in this data set, only one of the two covariates in each mood dyad was chosen to measure the active and passive dimensions of negative affect. The choice of variables was based on the woman's own retrospectively reported worst symptoms, or if she did not indicate which symptoms were worst, the variable with the greatest range of variation over the diary scale was taken.

6.5 Results

6.5.1 Discontinuation Rate

Forty-seven women enroled in the study, and thrity-six completed it. This represents a discontinuation rate of 23%. One might expect a high drop out rate in a study with such great demands, yet only about one third of women stopped the study due to what may be considered study side effects. Table 6.01 below summarizes the reasons for discontinuation.

Table 6.01 Reasons for Discontinuation from Cycle Manipulation Study

Reasons for drop out / discontinuation		**n=**
Study "side effects"	- worse PMS on Marvelon[1]	1
	- weight gain and ambivolence about study manipulations[6]	1
	- worsening of persistent nausea[4]	1
	- development of chronic breast tenderness and depression[5]	1
	Subtotal	**4**
Personnal factors or circumstances	- demands of study too great	1
	- break up of relationship, stopped pill[3]	3
	- house destroyed by fire[2]	1
	- family demands: ill health of father	1
	- delayed start therefore too late to finish	1
	Subtotal	**7**

Seven of these women dropped out of the study within the two month baseline period. All but one did so due to changes in personal circumstances which made it impossible to continue. One of the seven preceived her PMS to have worsened within the first month of taking Marvelon and discontinued as a result (1).

Five women persisted in the study for twelve weeks or more. One woman had to stop because her house was destroyed by fire (2), and another because her relationship ended and she wished to stop the pill (3). This second woman may also have been depressed (see discussion of BDI below). Three of the five who attemped to complete the study stopped due to effects that may either be attributed to the pill formulation or to adverse effects of cycle manipulations. One woman who had experienced nausea during the first week of the cycle on previous formulations, developed persistent nausea while taking Marvelon (4). She had been allocated to the continuous group. As a steroid sensitive person, prolonged pill taking probably contributed to her discomfort. I discontinued her from the study in week 14 as it seemed unethical to ask her to continue. She stopped using oral contraception and her nausea resolved.

Only two of the 11 drop outs stopped the study due to adverse effects that may be attributable to cycle manipulations. One woman was randomized to the continuous

group and the other was phase shifted. The first woman was a very busy travelling sales representative (5). She found it difficult to maintain the diaries and sample collection, and to keep appointments. The fact that she had very infrequent return visits probably contributed to her anxieties when she found that she did not have a bleed for a long interval. She reported that after the first "missed bleed" in week twelve she became progressively more unhappy and depressed, and she also had continuous breast discomfort and bloating. She had not been at all depressed previously. As will be shown below, this pattern is similar to a number of other women in the continuous group. The combined effect of these adverse symptoms and no reassurance in the form of "check ups" caused her to discontinue the study and stop taking the pill altogether.

The woman in the phase shifted group who dropped out did so because she had substantial weight gain that she believed was attributable to the study (6). She was also disconcerted by changes in the consistancy and volume of her bleeds, which she found darker and "stringy". In addition, she reported that her PMS which had been quite severe prior to entering the study was not coming at the normal time, and was lasting longer. Her experience was similar to others in the phase shifted group. The changed bleeds and disrupted mood cycles may be attributable to the cycle manipulation. She was already taking Marvelon when she entered the study, yet reported weight gain from the outset. The fact that she became 'symptomatic' without any change in pill formulation or regime implies that some of her reactions must be interpreted cautiously, as they may reflect false attributions.

6.5.2 Volunteer Characteristics

The demographic characteristics of the women who offered to be contacted for this study were discussed in the Chapter Four. The subsample who actually enrolled did not deviate markedly from those who did not. The mean age of continuing volunteers was 28.7 years. (SD 5.2), median age 28 years and range 19 to 41 years. These women had all used the pill for at least four months prior to entering the study. The mean length of pill use was 4.7 years (SD 3.9), the median 4 years, and the range 4 months to 15 years. Only eight women were smokers, and all of these were 33 years old or less. All women were of low parity, and most had never had a pregnancy: 29=para 0(0), 4=para 0(1), 1=para 1(0), 1=para 1(1), 1=para 2(1). The number of terminations are noted in parentheses. Figures 6.01 and 6.02 show the rank ordered distributions of age and duration of pill use respectively.

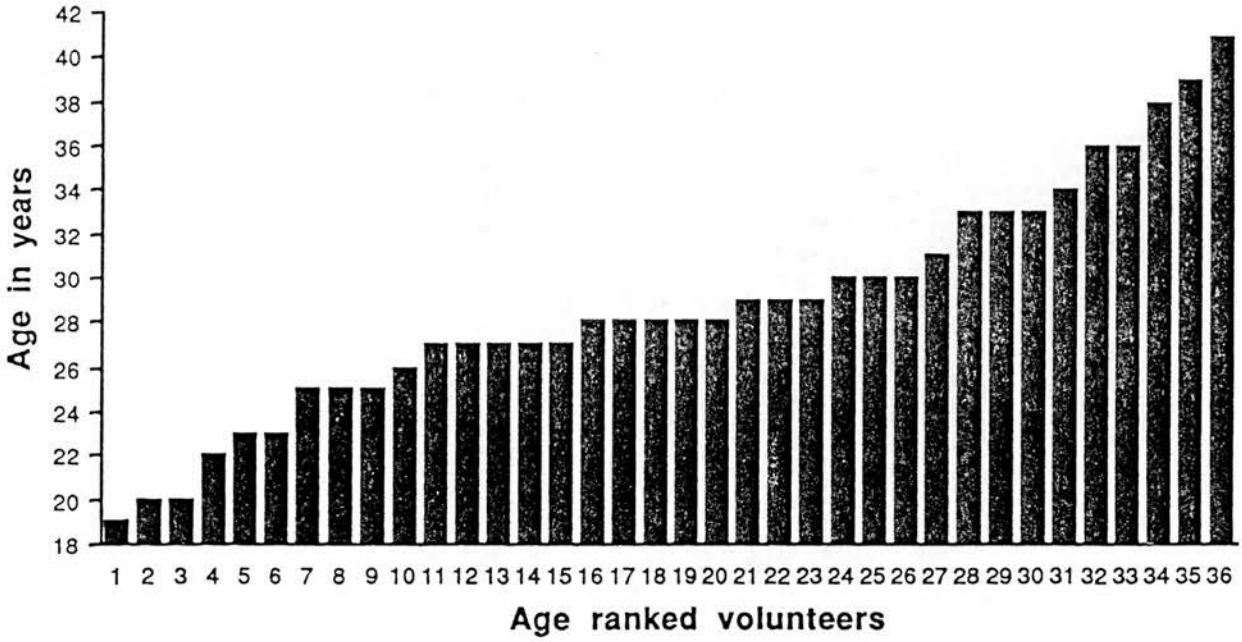

Figure 6.01 Ranked distribution by age of those women who completed the study.

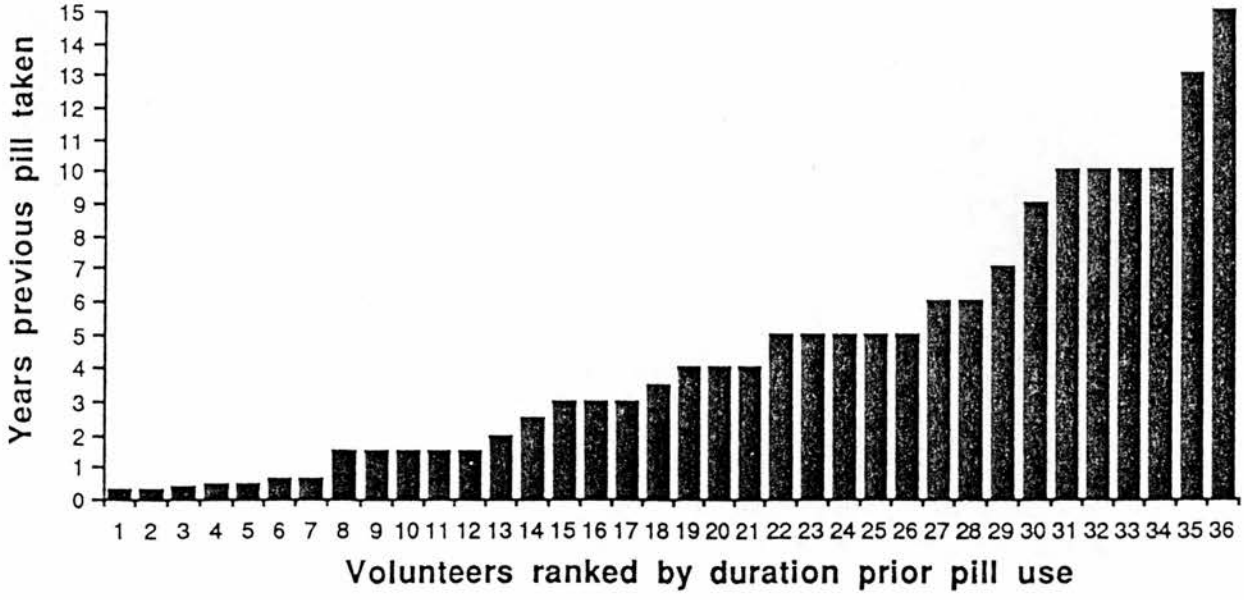

Figure 6.02 Ranked distribution by duration of prior pill use of those women who completed the study.

Table 6.02 COC pill types in use prior to entering study (Total n=36).

Monophasic Pill Name	Steroid Constituents	n=24
Brevinor	EE 35µg + NET 500µg	1
Microgynon / Ovranette	EE 30µg + LNG 150µg	14
Marvelon	EE 30µg + DSG 150µg	6
Mercilon	EE 20µg + DSG 150µg	2
Femodene	EE 30µg + GSD 75µg	1
Triphasic Pill Name	**Steroid Constituents**	**n=12**
Logynon / Trinordiol	EE 30µg + LNG 50µg (x5) EE 40µg + LNG 75µg (x6) EE 30µg + LNG 125µg (x10)	7
Trinovum	EE 35µg + NET 500µg (x7) EE 35µg + NET 750µg (x7) EE 35µg + NET 1000µg (x7)	5

Key: EE-ethinyloestradiol, NET-norethisterone, LNG-levonorgestrel, DSG-desogestrel, GSD-Gestodene.

Table 6.02 indicates that five-sixths of women had to switch to Marvelon from another combined pill formulation. Two-thirds of the sample were previously using a monophasic pill and one-third a triphasic. While the length of time that women had been taking their current formulation varied widely, 68% had taken it for at least two years, and over 80% for at least one year. This only describes the current pill used, and if previous formulations are considered, the duration of pill taking was longer for the majority of women. Thus, this sample of women can safely be considered established pill takers.

The distribution of retrospectively reported non-pill cycle lengths across the three study groups is summarized in Table 6.03. It is difficult to make a between group comparison as the group size is small. However, it appears without the benefit of a statistical test that the number of women showing short, regular, long, very long, and irregular cycles is similar in all three groups. The validity of women's self reported average cycle length has been called into question because of the difficulty many women have in accurately recalling or predicting the time of menstrual bleeds. While women are very good at anticipating the duration of the bleed itself, it seems that they are poor at predicting the inter-bleed interval (eg. Snowden & Christian, 1983). Thus important though information about usual menstrual cycle length is for testing the hypotheses of this study, this information is likely to be of limited value.

Table 6.03 Distribution of Previous Menstrual Cycle Lengths By Group Allocation

Group x Cycle length	Short: median <28 days	Regular: median ≈28 days	Long: median >28 days	Very long: length 42+ days	Irregular: range 14-50 days
Control	2	2	1	-	-
Continuous	2	9	3	1	1
Phase shift	1	7	4	2	1
Total	5 (14%)	18 (50%)	8 (22%)	3 (8%)	2 (5%)

6.5.3 Major and Minor Events: A Source of Potential Confounding

Very few women who took part in this investigation had an entirely trouble or stress free six months. A wide variety of events, major and minor, occured. Many of these experiences could have influenced subjective well being, and thus diary ratings. A number of women took a course of antibiotics at some stage which may have interfered with pill absorption, and thus effected hormone results. The commonly reported events are listed in Table 6.04. The total number is in excess of thirty-six because most women reported more than one event. Only three reported nothing at all. In subsequent analyses, note is made when a specific event was considered to have influenced diary ratings.

Table 6.04 Day to Day "Hassles" and Major Life Events Occuring During Study

"Life Event"	Number reporting
Minor ill health or operation	11
Course of antibiotics / corticosteroids	10
Foreign travel- including trans-continental	10
Relationship difficulties or break up	8
Work stressful	7
Moved house, bought or sold property	6
Started a new job	5
Got engaged or married	5
Death of a close relative	3
Partner or family member ill	3
Sister had baby	3
Self or partner made redundant	2
Started new relationship	2
Miscellaneous-alcohol abuse, death of aquaintance, assaulted at work, working night shifts, burgled, clinical depression and anxiety, pet died	1 each

Note: Some women reported more than one event.

6.5.4 The Effect of Cycle Length Manipulation on the Pattern of Vaginal Bleeding

The impact that systematic alteration in the length of the OC cycle has on women's experience of vaginal bleeding is of fundamental importance. Previous studies of the effects of prolonged pill taking have predominantly concerned themselves with the question of its acceptability to women. This acceptability is intimately linked to the efficacy of these manipulations in postponing bleeds. Women who experience a great deal of breakthrough bleeding (BTB) are less satisfied with manipulation, and have been more likely to drop-out of studies (Loudon, et al., 1977; Hamerlynck, et al., 1987; de Voogd, 1991; Kornaat, et al., 1992). Therefore, it is important to consider the bleeding experience of these volunteers in order to interpret their other diary ratings, and to ascertain the potential acceptability of very long cycles. If extended cycles were to have a favourable effect on cyclical negative affect, for example, women still might not choose this as a PMS treatment if it grossly altered their pattern of bleeding.

The total number of breakthrough and withdrawal bleeding days by group was close to that predicted given the pill taking regime. The mean number of days bleeding per woman in each group is shown in Figure 6.03. Figure 6.04 is a periodogram of the bleeding experience of all the women who completed the study. Unlike scheduled withdrawal bleeding, the patterns of BTB were quite different in the three groups. Overall 10 out of 36 women had BTB in the baseline months: control 1/5, continuous group 2/16, phase shifted 7/15.

BTB was relatively consistant over time in the phase shifted group; seven of the eight women who had it in the baseline had further BTB later in the study. The continuous group however, who had virtually no BTB in the baseline had an exponential increase in the number of bleeding days as the study progressed. Eleven out of sixteen women in this group had BTB during the protracted cycle, and in the fouth month of continuous pills, 9 women had more than 100 days of bleeding between them (see Figures 6.05 and 6.06).

6.5.5 Hormonal Results

All of the ßhCG tests conducted for this study were negative. There were no pregnancies. There was considerable anxiety about pregnancy, but the tests reassured women.

Twenty-five of the 36 women who completed the study collected urine samples: 5/5 controls, 8/16 continuous, 12/15 phase-shift. All samples were assayed for E-3-G in the manner described above. The pattern of oestrogen that these women showed during the first 11 weeks of the study was very similar to that of the Microgynon/Ovranette and Logynon/Trinordiol takers in the folliculogenesis study. Because samples were not collected on the same study days by all volunteers weekly group means are reported. Figure 6.07 compares the E-3-G profiles for all three groups in the baseline weeks. (Three women in the phase-shifted group have been excluded- see below) All groups show a typical profile of rising E-3-G during the withdrawal bleeding intervals in weeks 4 and 8, and peak levels in the first week of pill taking in weeks 5 and 9. Oestrone levels return to the post-menopausal range by the second consecutive week of pills where they remain until the next withdrawal week. There was no significant difference between the three groups in the first 11 weeks

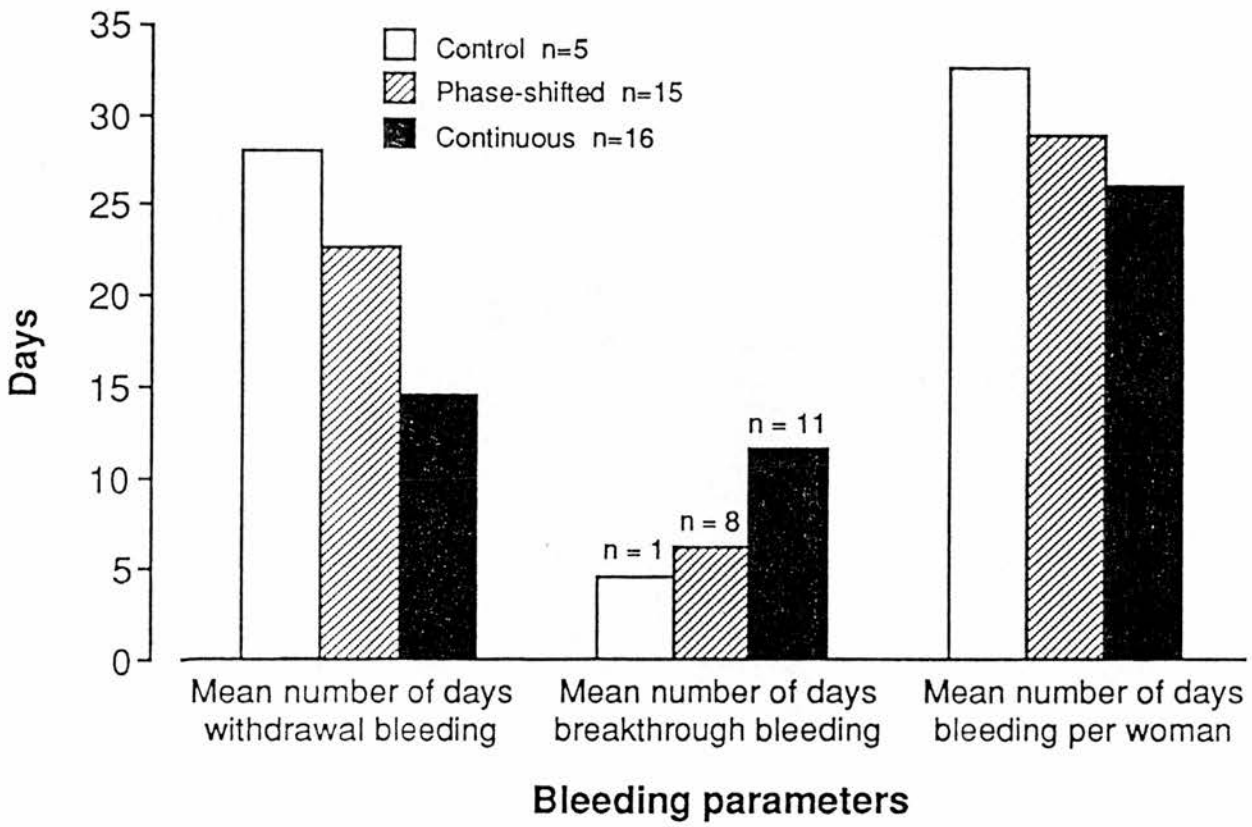

Figure 6.03 Effects of cycle length manipulation on the mean number of days bleeding by group.

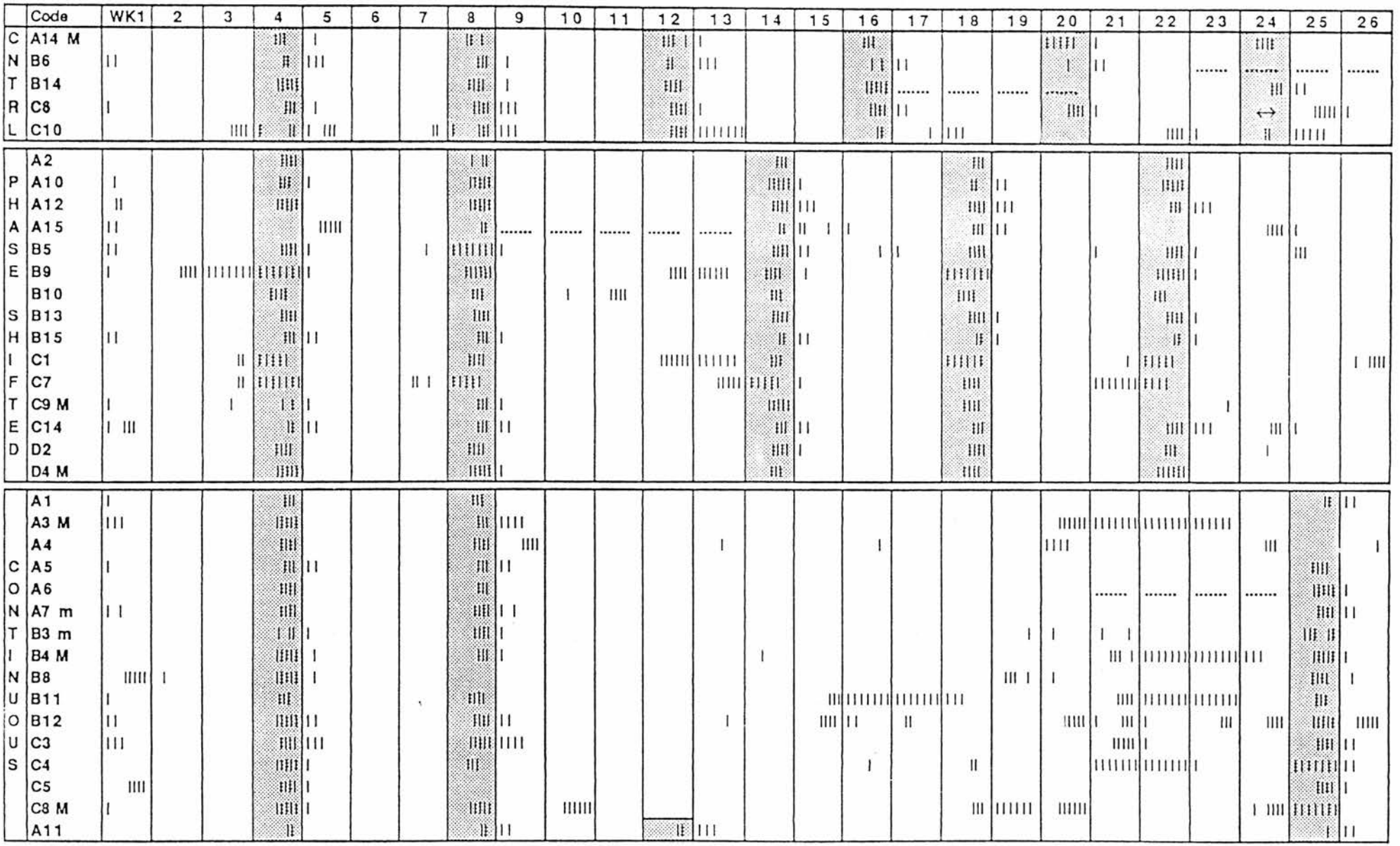

Figure 6.04 Periodogram of the bleeding experience of each individual study participant over 26 consecutive weeks.

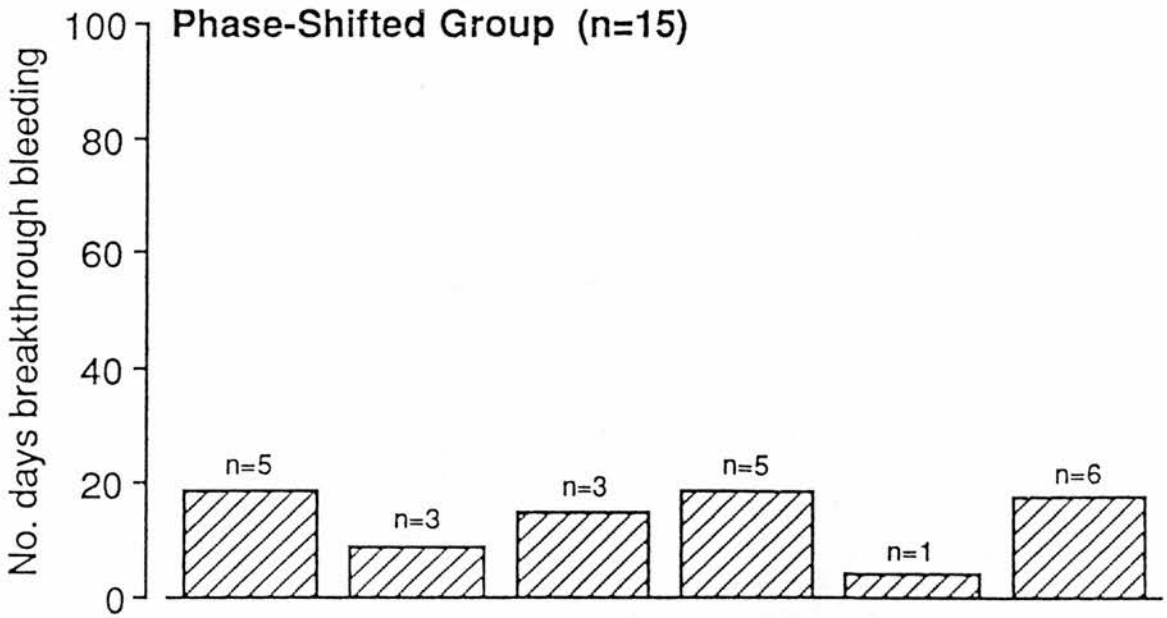

Figure 6.05 Total number of days of breakthrough bleeding occurring during active pill taking over the six study months in the phase shifted group.

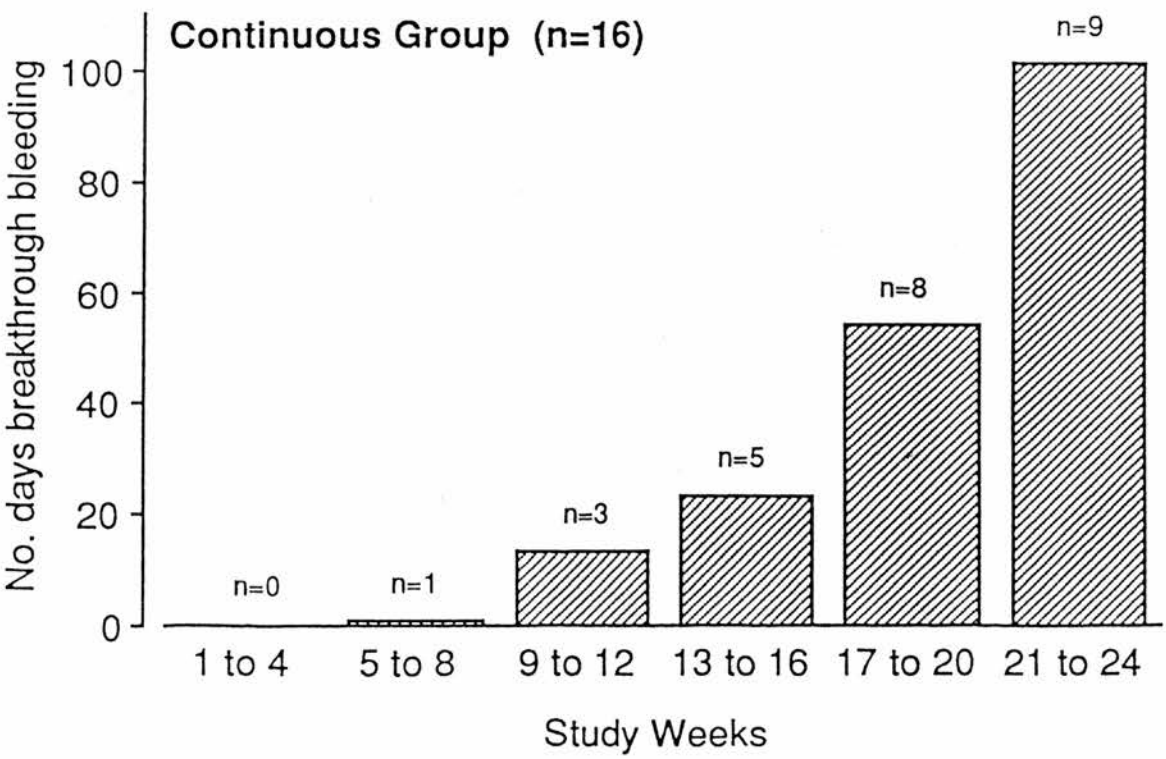

Figure 6.06 Total number of days of breakthrough bleeding occurring during active pill taking over the six study months in the continuous group.

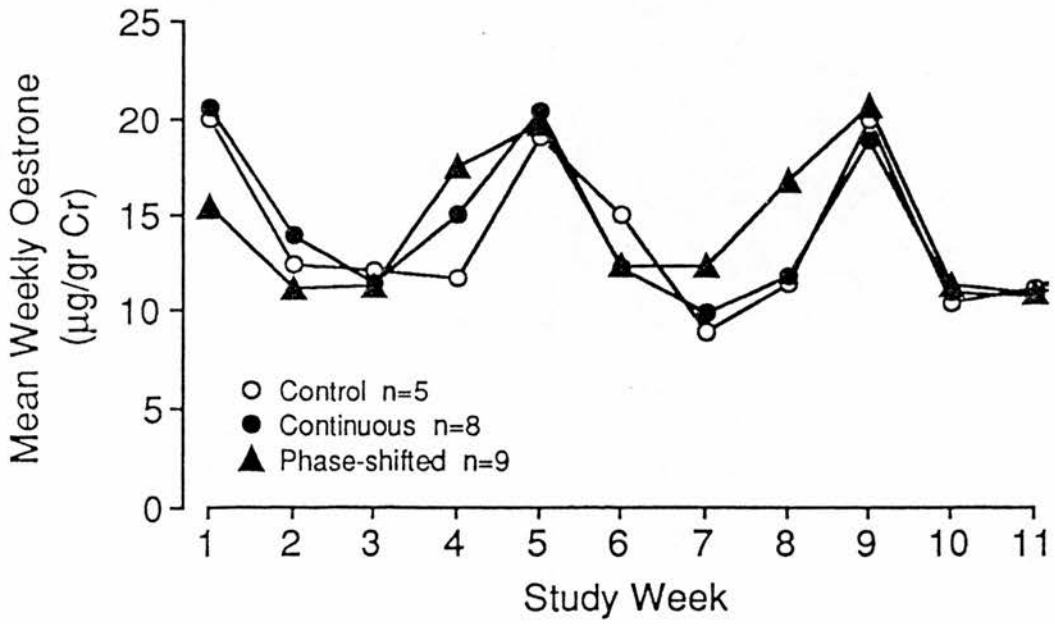

Figure 6.07 Comparison of weekly mean oestrone levels across all three study groups during the 11 baseline weeks.

(Control vs. Continuous t=-0.20, p=0.84; Control vs. Phase shifted t=-0.41, p=0.68; Phase shifted vs. Continuous, t=0.20, p=0.84).

This pattern continues for the remainder of the study for the control group[3]. Those women who collected samples in the continuous group showed quite homogeneous profiles. When the withdrawal bleeding intervals were abolished so too was escape ovarian function. After a low mean peak in week 9 there were no further notable rises in E-3-G, and levels remained at a post-menopausal baseline for the remainder of the study. (See Figure 6.08) Only half of the continuous group provided samples, and it is possible that the other half would have shown a different degree of ovarian function.

The pattern of the phase shifted group, shown in Figure 6.09, is more complex than the other two, and runs counter to expectation in a number of ways. In week 12, when a bleed would have occurred had there not been a phase delay, E-3-G showed a transient rise. Levels returned to baseline in week 13, but rose again in the actual withdrawal week, 14, and peaked in the first subsequent active week. The profile after the next two withdrawals was similar to the baseline.

Student's t-tests comparing the oestrone profiles of the groups in the second half of the study (weeks 9-25) showed that the control and phase-shifted groups were not significantly different from one another (t=-0.53, p=0.59), while the control and continuous (t=3.11, p<0.00), and continuous and phase shifted (t=-3.10, p<0.00) were. These results are consistent with the visible differences between the mean profiles of the three groups, and with the exogenous steroid regimes administered.

The oestrogen results of three women in the phase shifted group were excluded from the group mean because they were markedly different from the remainder of the group. Volunteers B10, C7, and D4 each had peak E-3-G values which were ten-fold higher than the mean of the other 9 women in this group. Figure 6.10 shows the daily E-3-G measures for these women. The peak levels which they achieved were at least equal to, if not substantially greater than, the E-3-G levels which one sees around ovulation in the normal menstrual cycle. Furthermore, each woman showed a sustained rise in E-3-G over many days during more than one cycle, over the six months. These

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3
It becomes less distinct because one woman stopped collecting samples in week 13, a second missed samples during the would-be peak weeks 24 and 25, and a third (C10) had raised E-3-G at unusual times relative to withdrawal weeks.

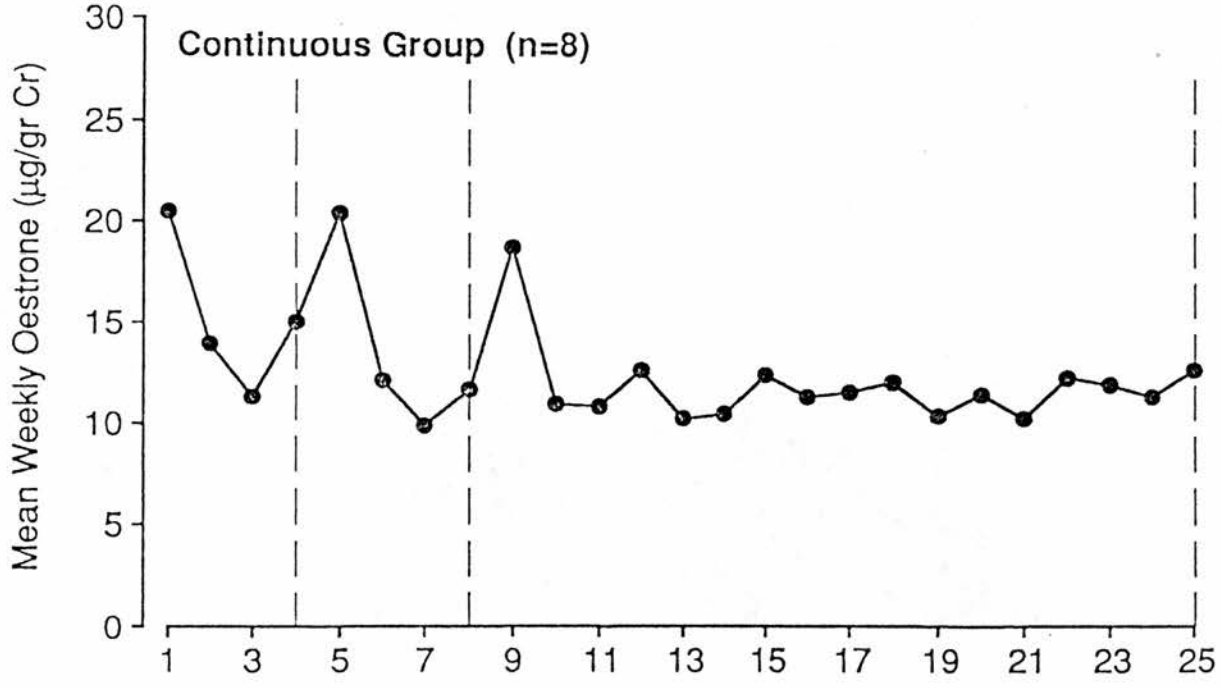

Figure 6.08 Weekly mean oestrone levels during the entire study in the continuous group.

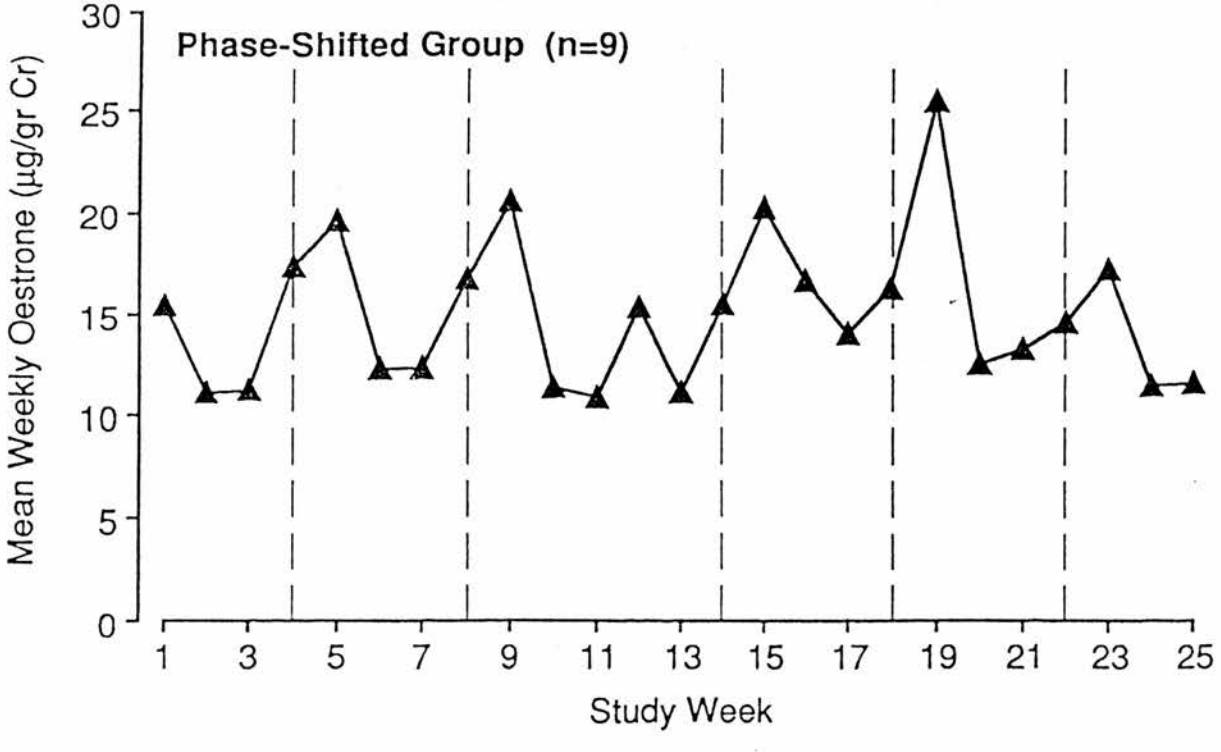

Figure 6.09 Weekly mean oestrone levels during the entire study in the phase shifted group.

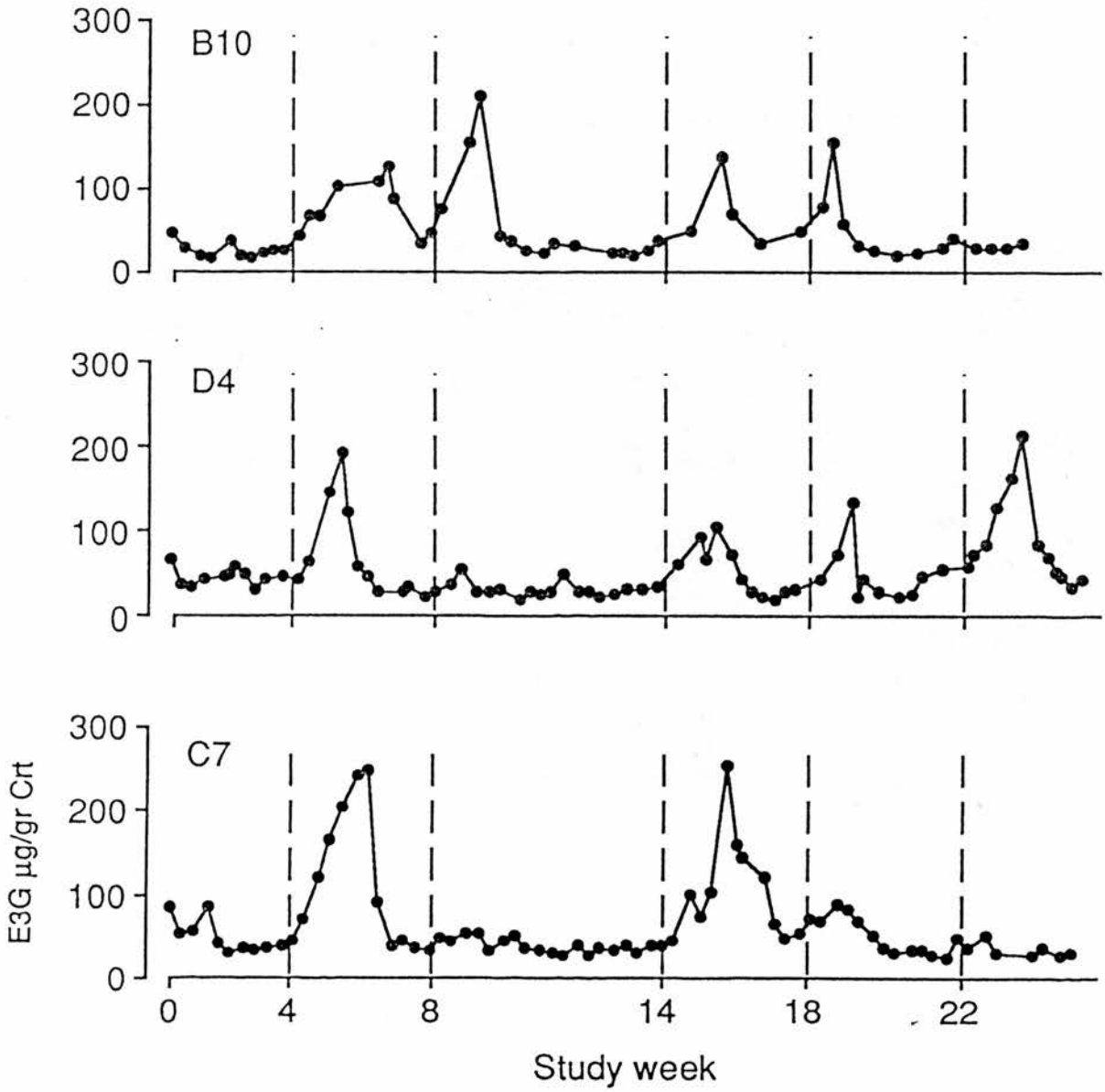

Figure 6.10 Individual oestrone profiles for three women in the phase shifted group who showed markedly elevated levels of oestrone.

extended and repeated rises in E-3-G within three separate individuals imply that this is not an artifact of assay error or poor sampling technique[4]. The lowest values are similar to the baseline levels shown by all the other pill takers in this thesis, reflecting that the samples covered the whole range of the assay.

Pregnanediol levels were assayed in "spot" samples in the manner described above for these three women, in each of the ten cycles in which E-3-G was raised. No pregnanediol level was high enough to indicate that ovulation may have taken place, and it was concluded that, although reflecting substantial folliculogenesis these cycles were anovulatory.

6.5.6 Final Assessment

This section describes the self-reported retrospective experience of the study. Tables 6.05 to 6.09 summarize changes in emotional and physical well being and bleeding parameters reported by the three groups of women on the study assessment form. "Postive affect / energy" relates to the sentence completions for "happy" and "energy" on the form. "Negative affect" includes "bad tempered", "mood swings", "depressed", and "tense". If a woman reported at least one of these she was included in the appropriate category. No individual's responses were divided- e.g. more depressed, but less tense.

4
Isolated spikes are sometimes observed in urinary steroid profiles when a sample has been taken late in the day, and is therefore very dilute. A "watery" sample will have a very low creatinine reading. It will also have to be used at a lower than normal dilution in the ELISA, possibly "neat", and will thus be susceptible to interference and an inflated reading. This produces a distorted E-3-G/Crt ratio in "one off" samples, but cannot explain the protracted rises seen here.

Table 6.05 Retrospectively reported change in mood and physical state in the control group (n=5).

Symptom	More	Less	None or Same as Before
PMS	1 (20)	-	4^{M} (80)
Positive Affect / Energy	-	-	5^{M} (100)
Negative Affect	3^{M} (60)	-	2 (40)
Sexual interest	-	2^{M} (40)	3 (60)
Breast tenderness	-	-	5^{M} (100)
Bloating	2^{M} (40)	-	3 (60)
Weight gain	2^{M} (40)	n/a**	3 (60)
Headaches	1 (20)	-	4^{M} (80)
Period type pain	-	2^{M} (40.0)	3 (60)

One of those women who experienced symptoms was already taking Marvelon when she began the study, and her experience of symptoms is denoted by the symbol - ^{M}.
** The questionnaire was not worded to allow women to indicate if they had lost weight. Percentages are shown in parentheses.

The control group shows that certain effects may be attributed to the Marvelon itself, or to the influence which simply taking part in the study had on well being. None of the controls reported any increase in happiness or energy, but three noted more negative affect. Two reported more tension (A14 & C6) and one had more irritability and mood swings (B14). One woman (A14) who described more tension along with weight gain, more bloating, and less sexual interest was already taking Marvelon prior to entering the study. She had changed neither OC formulation nor regime, therefore, the symptoms she experienced must be attributable to other causes.

The woman who was more irritable (B14) indicated in her final interview that she had only had these feelings initially, and attributed them to a fear of the unknown. She believed that she was more anxious because she was blind to the timing of her bleeds. Once she had had several bleeds at the "normal" intervals she decided that she was probably a "control" and had no further negative mood. Both of these cases suggest genuine study effects.

Changes in physical well being are less likely to result from anxiety about study effects and more likely to be a consequence of the switch to a new pill. Yet the Marvelon taker noted a number of physical changes too. It could be chance that some of the controls

felt physically different during this six months. Alternatively, diary keeping might have peaked awareness. The control groups experience dictates that caution should be used in interpreting the cause of such changes in the other groups. Negative study effects here may be a function of the unique nature of this investigation; notably that concealling the time of bleeding from women seems to cause anxiety.

Table 6.06 Retrospectively reported change in mood and physical state in the continuous group (n=17*).

Symptom	More	Less	None or Same as Before
PMS	1 (6)	6^{m} (35)	10^{MMMm} (59)
Positive Affect / Energy	4^{m} (24)	4^{m} (24)	9^{MMM} (53)
Negative Affect	9^{Mm} (53)	6^{m} (35)	2^{MM} (12)
Sexual interest	4^{Mm} (24)	4^{m} (24)	9^{MM} (53)
Breast tenderness	7^{Mm} (41)	2^{M} (12)	8^{Mm} (47)
Bloating	10^{MMMm} (59)	4^{m} (24)	3 (18)
Weight gain	11^{Mm} (65)	n/a**	6^{MMm} (35)
Headaches	4^{m} (24)	3^{m} (18)	10^{MMM} (59)
Period type pain	2^{M} (12)	4 (24)	11^{MMMm} (65)

* Note that this number includes one woman who dropped out of the study from this group in week 18; she is not included in the assay or diary data analyses.
3 women in the continuous group were taking Marvelon when they began the study, and their experience of symptoms is denoted by the symbol - ^{M}.
2 further women were taking Mercilon, which has 10µg less EE than Marvelon; their experience of symptoms is denoted by the symbol - ^{m} .
** The questionnaire was not worded to allow women to indicate if they had lost weight. Rounded percentages are shown in parentheses.

Table 6.07 Retrospectively reported change in mood and physical state in the phase shifted group (n=15).

Symptom	More	Less	None or Same as Before
PMS	3 (20)	6^{M} (40)	6^{M} (40)
Positive Affect / Energy	3^{M} (20)	2^{M} (13)	10 (67)
Negative Affect	4^{M} (27)	5^{M} (33)	6 (40)
Sexual interest	1 (7)	2 (13)	12^{MM} (80)
Breast tenderness	4^{M} (27)	2 (13)	9^{M} (60)
Bloating	3 (20)	-	12^{MM} (80)
Weight gain	4^{M} (26)	n/a**	11^{M} (73)
Headaches	4^{M} (27)	2^{M} (13)	9 (60)
Period type pain	5 (33)	3^{M} (20)	7^{M} (47)

2 women in the phase shifted group were taking Marvelon when they began the study, and their experience of symptoms is denoted by the symbol - ^{M}.
** The questionnaire was not worded to allow women to indicate if they had lost weight. Rounded percentages are shown in parentheses.

As one might expect, the two manipulated groups reported higher incidences of change in their well being than the control group. Between 20 and 40% of women in these two groups described feeling better during the study months with less PMS, happier/ more energy, and less negative affect. About an equal proportion in the phase shifted group, however, and over half of the women in the continuous group noted more negative moods. The two manipulated groups also had substantial proportions of women who seemed to be worse off physically. This was particularly marked in the continuous group in which over 40% of women reported more breast tenderness, bloating and weight gain, and about one quarter less sexual interest and more headaches.

Table 6.08 Self-reported bleeding pattern.

Group	Withdrawal Bleeding	More	Less	Same
Control	Volume	1 (20)	1 (20)	3^{M} (60)
(n=5)	Duration	-	3 (60)	2^{M} (40)
Continuous	Volume	6^{MM} (35)	6^{M} (35)	5^{mm} (29)
(n=17*)	Duration	4 (24)	3^{m} (17)	10^{MMMm} (59)
Phase shifted	Volume	4^{M} (27)	3 (20)	8^{M} (53)
(n=15)	Duration	3 (20)	3 (20)	9^{MM} (60)

* Note that this number includes one woman who dropped out of the study from this group in week 18; she is not included in the assay or diary data analyses.
3 women in the continuous group were taking Marvelon when they began the study, and their experience of symptoms is denoted by the symbol - ^{M}.
2 further women were taking Mercilon, which has 10µg less EE than Marvelon; their experience of symptoms is denoted by the symbol - ^{m}. Rounded percentages are shown in parentheses.

Table 6.09 Comparison of the retrospectively reported incidence of breakthrough bleeding.

Group	A lot of BTB	Some BTB	A little BTB	No BTB
Control (n=5)	-	1 (20)	-	4^{M} (80)
Continuous (n=17*)	1^{M} (6)	3^{M} (17)	7^{m} (41)	6^{Mm} (35)
Phase shifted (n=15)	-	1 (7)	5^{M} (33)	9^{M} (60)

* Note that this number includes one woman who dropped out of the study from this group in week 18; she is not included in the assay or diary data analyses.
3 women in the continuous group were taking Marvelon when they began the study, and their experience of symptoms is denoted by the symbol - ^{M}.
2 further women were taking Mercilon, which has 10µg less EE than Marvelon; their experience of symptoms is denoted by the symbol - ^{m}. Rounded percentages are shown in parentheses.

Tables 6.08 and 6.09 summarize the retrospectively reported bleeding experience of the study participants. Overall about half the women who completed the study reported some change in the volume, duration, or pain associated with bleeding. A slight majority of women noted that while their bleeding was heavier, it tended to be shorter and less painful. Eighteen volunteers indicated that they had had BTB at some time during the six months. Thus more than half the women taking part experienced 'irregular' bleeding or spotting. In fact, the completed diaries indicate that 20, rather than 18 women had bleeding during active pill taking. The discrepancy may be due to

poor recall, very minor amounts of BTB, or it may be because some women actually believed their break-through-bleeds were "proper periods". At least two women did report that they were having "periods" when they were in fact having BTBs.

6.5.7 Clinical Monitoring

The monthly interview notes gave the volunteer's perspective on the effects of the manipulations. Four women in the continuous group who had previously experienced cyclical well being over the pill cycle, with negative affect prior to bleeding, reported relief from symptoms during the protracted cycle. One woman (B3) who suffers from PMS and her fiancé both noticed a marked improvement in her moods during the protracted cycle. She described it as being more "level", "even", "less up and down". Another woman (C3) reported more breast tenderness and weight gain, but although she had expected to have PMS even if she were not bleeding monthly, she commented that she had had "no PMS at all" during the study.

A third woman (C5) indicated that she had felt very well during the protracted cycle, and that she enjoyed not having periods. Both she and her husband believed that the study had helped to improve her moods substantially, and she had also had none of the usual pain or bloating. She described "tremendous" chocolate craving before her final withdrawal bleed in week 25. The fourth woman (A5) was experiencing quite profound PMS when she entered the study. Yet after the first baseline cycle she reported that her moods were very steady and she did not feel "premenstrual" at all. She described the improvement as "no' always beeing ready to swing for people."

A second group of three women in the continuous group continued to report having cyclical symptoms at intervals although the hormone regime was constant. One woman (B8) noted that she had "all the signs" of a coming period, including tearfulness, spots, and bloating, during the first missed withdrawal bleed in week 12. These symptoms of a period spontaneously resolved after a few days. She "was fine" in week 16, but she "felt like" she was going to have a period in weeks 19 and 20, and an episode of spotting followed. The second woman (C4) reported "feeling very premenstrual" in weeks 15 and 24. Her symptoms included her usual pattern of moodiness, constipation, and indigestion. These "premenstrual" episodes correspond to the fourth would-be premenstruum, and the sixth would-be withdrawal bleeding phase. The third woman (B12) found that her mood was very "up and down" from weeks 8 to 19 of the

study. For example, in week 19, which was the fourth would-be premenstruum, she was "very depressed", then felt "euphoric" for a few days before having a six day BTB in week 20. She was one of the volunteers who believed that she was having regular withdrawal bleeds, although it was actually BTB.

Over half of the women in the phase shifted group reported experiences which seemed to indicate the presence of some sort of ghost cycle, and/or a general disruption in the timing of cyclical changes brought about by the phase shift. The pattern of fluctuations in subjective state after the phase shift often seemed to be different from what it had been before, and in many cases physical and mood states became dissociated. One woman (A8) who normally had severe negative mood change before bleeding, and who dropped out of the study because of the effects which it had on her (see case 6 in Table 6.01 above) felt that she was "premenstrual for most of the month" during the 6-week phase shifted cycle. She reported that after the bleed in week 14 her negative affect peaked and dissipated several times without associated bleeds. She said that, "the study has put me a week ahead of myself with PMT."

Another phase shifted woman (C9) felt bloated, and "had a discharge" during the would-be bleeding week 12, and then felt irritable at irregular intervals throughout the remainder of the study. She was already on Marvelon, and had formerly had her most irritable phases premenstrually. One woman (C1) bled in both weeks 12 and 14, and again at the would-be bleed time in week 26. She also had period pain, but no bleeding in week 19.

Another woman (D2) was tired in week 12, but "had no PMS", yet became "moody and irritable" a few days before the withdrawal bleed in week 14. She then had period pain in week 16 but no bleed. In week 26 when a bleed was "due" but did not occur because the packet of Marvelon had been added straight on, she felt like she should be having a bleed as she "had period pain and headaches, and was grumpy."

Two more women who normally experience PMS symptoms before their bleeds found the timing had changed. One (B15) had all the usual physical symptoms prior to bleeds from the beginning of the study, but no "PMT day". Her "PMT day" previously fell predictably on day 19 of a pill packet, about 7 or 8 days prior to bleeding, yet she did not have one in the study until week 16, 12 days prior to the next bleed. She then had another "PMT day" 11 days later, one day before the week 18 withdrawal bleed. She

had still others for one day each in weeks 24 and 26. The second woman (B9) noted in week 12 that she had had "all the signs that it was due", but only had spotting, and then a "proper period" in week 14. Again in week 24, when a would-be bleed should have been, she felt depressed and tense, but did not have another actual withdrawal week for a further four weeks.

The data provided here are retrospective and anecdotal. However, they give some suggestive evidence that certain women experienced persistent cyclicity in subjective state during continuous pill administration. In others, cyclical changes were damped down or disappeared. Reports from the phase shifted group indicate that the timing of cyclical changes in relation to withdrawal bleeding can be successful altered by "moving the period". For a number of women changes that formerly only happened before a withdrawal bleed began to happen at other times of the cycle after the phase shift.

Contrary to the initial hypothesis, physical changes did not appear to be more closely bound to variations in exogenous steroid levels than mood changes. This is reflected by the fact that a number of women experienced period pain in the absence of any bleeding or of a placebo week. Breast tenderness seemed to be more severe and persistent in the extended groups, and may be more steroid dependant than other physical changes.

6.5.8 Results of Prospective Daily Diaries

The daily diary data are summarized in this section according to the descriptive techniques which were outlined in section 6.4.6.2 above.

6.5.8.1 The severity and timing/cyclicity of selected diary variables in the control group

Six women were allocated to the control group. However, one woman had to be single-blindly switched to the continuous group in mid-study (her case will be discussed later), so ultimately there were only 5 controls. At the beginning of the study two of these women reported that they did not have PMS or any notable cyclical change in their well being. A further two reported mild emotional and physical changes, while one presented as a PMS sufferer. Yet on inspection of the plots of selected diary variables over time, the only symptoms which showed any marked regularity for the

four women who had retrospectively reported no changes or mild PMS were period pain and bleeding itself.

Theoretically, no symptom should have changed in severity at all over the study in this group since they underwent no manipulation of their cycle. Table 6.10 below summarizes the number of women in the control group who showed either a statistically significant increase, decrease, or no change in the mean severity of each variable in a Student t-test between the two baseline months and the four "treatment" months. This table shows that there were changes in the control group over time. One control each showed a decrease in the 4 physical symptoms. Three of these four women had switched to Marvelon for the study, but the woman whose diaries showed less marked bloating over time was already taking Marvelon before she entered the study. Curiously this was the same woman who noted on her final assessment form that she had been more bloated during the study. So there is a contradiction between her retrospective and prospective assessments of this symptom. We must therefore be cautious when interpreting the cause for changes in symptom severity in the two manipulated groups.

The most notable finding is that all the controls were less irritable after the first two months. This would seem to confirm that taking part in the study, initially had a negative effect on volunteers, but over time with regular bleeds this effect wore off. This could be due to anxiety and hightened awareness due to diary keeping, double-blindness, or it could reflect the settling-in period on a new pill formulation. The profile for irritability for four of the controls in Figure 6.11 shows the tendency for scores to be higher in the first two months of the study.

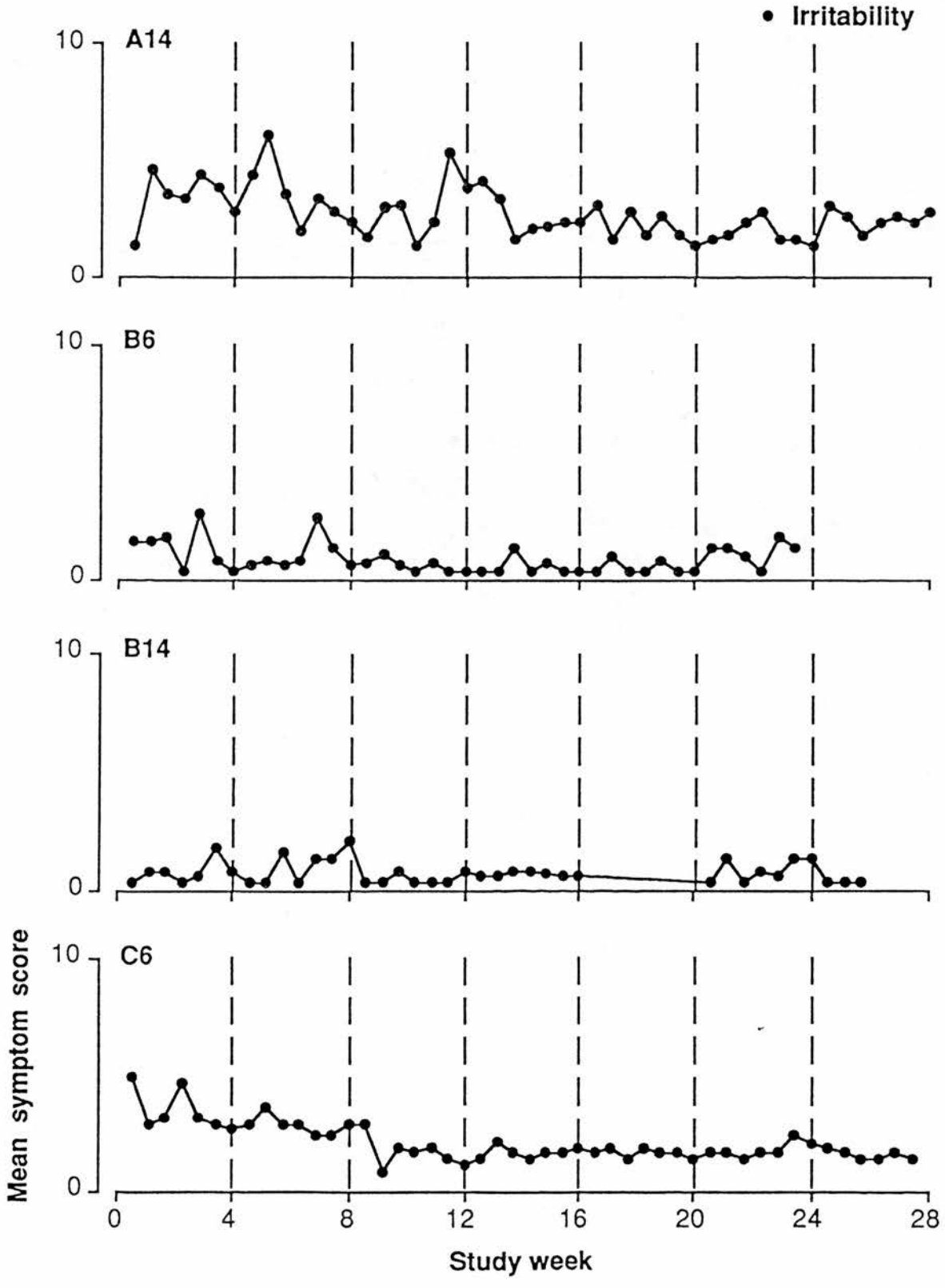

Figure 6.11 Individual phased profiles of irritability for four women in the control group. Dotted lines indicate the position of the pill free interval.

Table 6.10 Control Group: Number of women showing significant difference ($p<0.05$) in mean diary score from baseline to "manipulation" on Student t-test

Direction of Change	Bleeding	Period type pain	Irritability or Anger	Depression or Tension	Breast tenderness	Bloating
no change	4	4	-	2	4	3
more	-	-	-	1	-	1
less	1	1	5	2	1	1

The fifth woman who considered herself a PMS sufferer, was the only one in the control group who showed a predictable relationship between her well being and her endogenous steroid and bleeding patterns. Both her pattern of bleeding and her oestrogen profile were irregular for a pill taker. Rather than showing consistent withdrawal bleeds within a few days of starting a dummy pill week, her bleeds started while still taking active pills or did not occur during the dummy pill week at all. Her oestrone levels were also relatively high and do not show the classical post-menstrual rise and rapid return to baseline demonstrated in Chapter Three.

Figure 6.12 shows the profile of a number of her symptoms. Note the relationship of peaks in irritability and breast tenderness to subsequent bleeds whether scheduled or breakthrough. Note also the elevation in the baseline level of bloating, which though higher still oscillates in time with bleeds. The profile for depression which is not shown was similar to irritability.

None of the controls showed a robust cyclical pattern, therefore their usefulness as a baseline for steroid cycle linked cyclical change is limited. This problem was probably produced by small numbers and by the fact that women were not chosen to take part in this study because they reported cyclical changes, but recruited on the basis of their pill taking and willingness to undergo cycle manipulations. Fortunately, the women in the "experimental" groups may serve as their own control because they experienced two conventional four week cycles prior to manipulation.

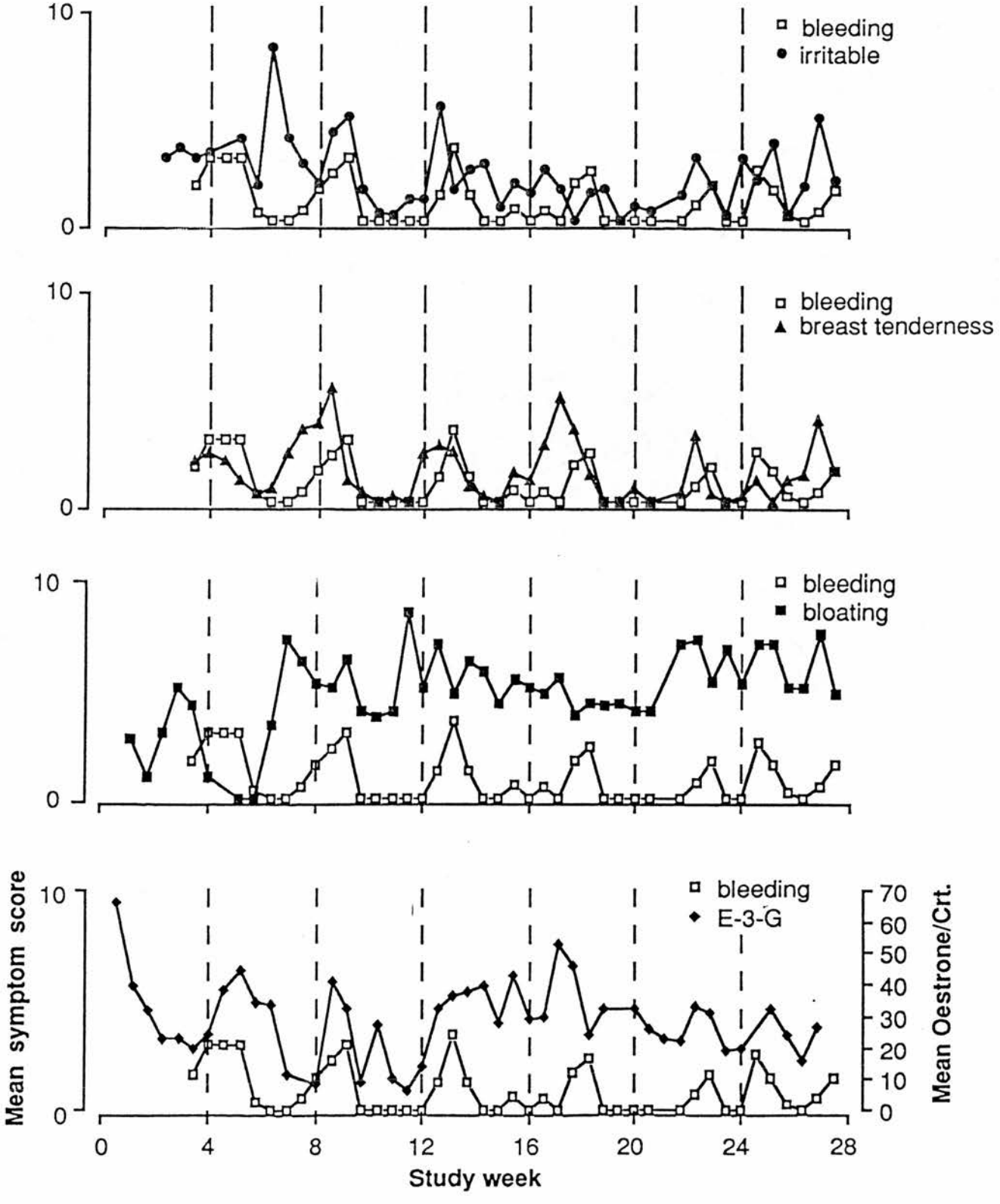

Figure 6.12 Profiles of selected mood and physical variables in relation to bleeding for control C10. Dotted lines indicate the position of the pill free interval.

6.5.8.2 The severity and timing/cyclicity of selected diary variables in the continuous group

The responses of women to constant pill taking were not uniform. A number of patterns of symptoms emerged from the diary ratings. When the diary data of the 16 members of this group were examined a number of idealized models were kept in mind that might describe the patterns in the data. These models were developed based on various potential aeitiolgical theories for the existence of cyclical change in well being. They were designed to categorize similar responses to the manipulation, but in practice proved too inflexible and arbitrary to be of practical use. However, for their theoretical interest they are reproduced in Appendix 6.15.

A number of patterns did in fact emerge from the data itself. If this group were to show persistent oscillation in well being with constant pill administration in precisely the same manner that they do during conventional cycles then one would expect no change in overall mean symptom severity. Alternatively if symptoms occurred only around the time of withdrawal bleeding then one would expect all of the means to be significantly lower in the second half of the study, since there is only one scheduled bleed. The table below demonstrates that neither is the case.

If bleeding and period type pain were purely a function of steroid withdrawal then one would expect lower mean levels in the second half of the study However many women did not show a change in the mean amount of these variables. This may reflect the fact that a large proportion of women in the group had significant amounts of breakthrough bleeding. But an even larger number have no change in period pain, which suggests that period pain occurred in the absence of bleeding for some women.

Table 6.11 Continuous Group: Number of women showing significant difference ($p<0.05$) in mean diary score from baseline to "manipulation" on Student t-test

Direction of Change	Bleeding	Period type pain	Irritability or Anger	Depression or Tension	Breast tenderness	Bloating
no change	7	11	11	8	7	8
more	-	-	1	5	6	5
less	9	5	4	3	3	3

The mood symptoms are more difficult to interpret. But it is clear that a much smaller percentage of this group than the controls had improved mood as the study progressed. And quite a number of women actually became more irritable or depressed. The distribution of significant changes in breast tenderness and bloating were very similar to depression, with about a third of women scoring higher breast tenderness and bloating in the second half of the study.

On examination, the diary data of 4 of the 16 women was deemed to be of limited interest because symptom levels were too low or too erratic to interpret, or data were missing. For the remaining 12 it became evident that a number of women showed similar patterns of symptoms. There were four groups of three women each who showed consistent patterns of symptoms to one another. The probability that different women will experience one symptom in a similar way over six months is remote, but it is even more unlikely that they will be similar for more than one symptom concurrently. So although conventional statistics connot be readily applied to this data, the repetition across women implies a genuine effect.

A) Symptom subgroup one. The first group is made up of volunteers A7, B4, and B12. Figures 6.13 to 6.15 show their symptom profiles over the entire study. In these and subsequent figures one mood variable is shown as an illustration, along with the four physical variables. In this subgroup negative mood, notably depression seemed to become chronic as the study progressed. One woman (A7) described it as being like an endogenous depression. The three physical symptoms, breast tenderness,

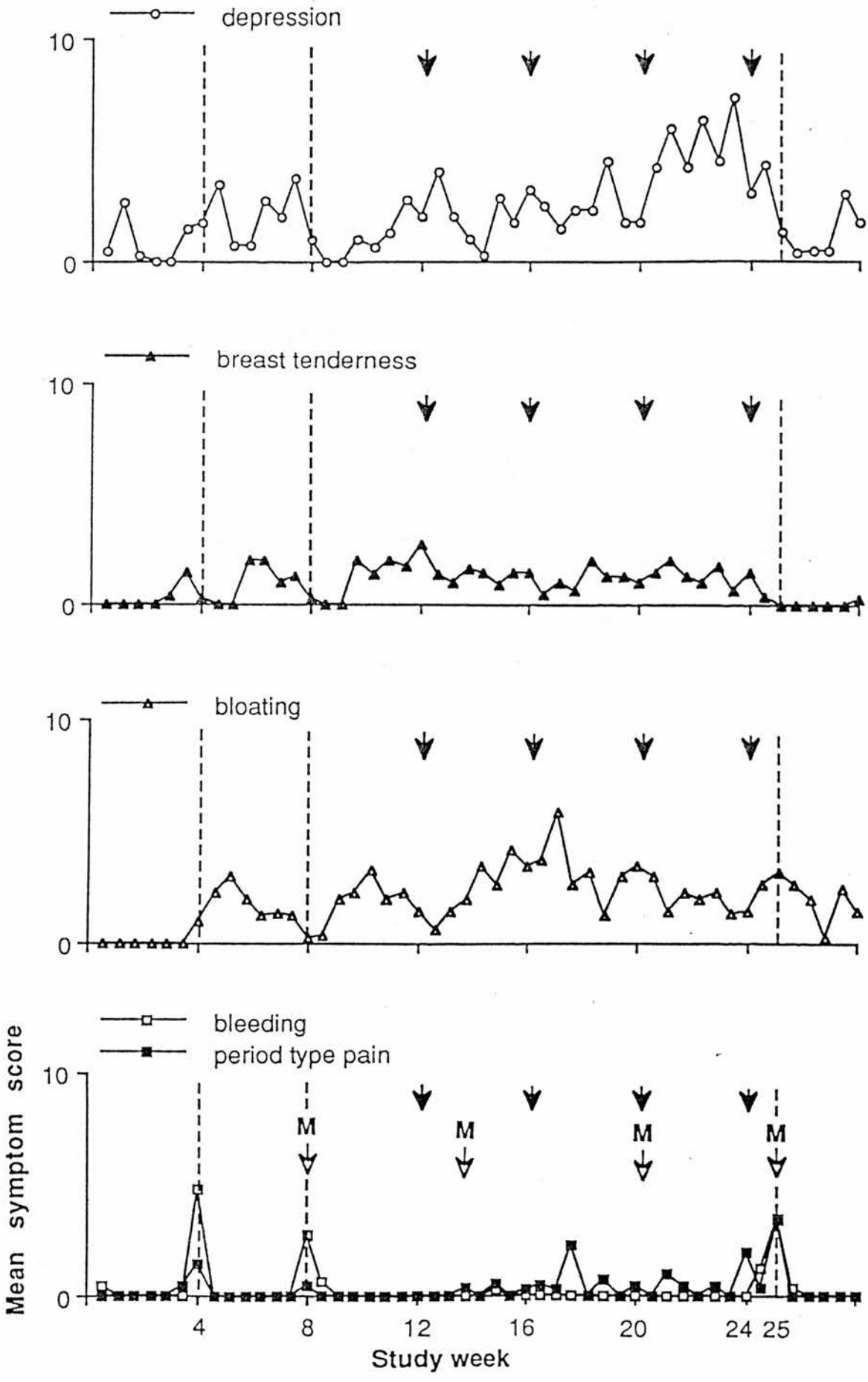

Figure 6.13 Symptom subgroup 1. Profiles of selected mood and physical variables for continuous group member A7. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds. Open arrows indicate the position of migraine headaches.

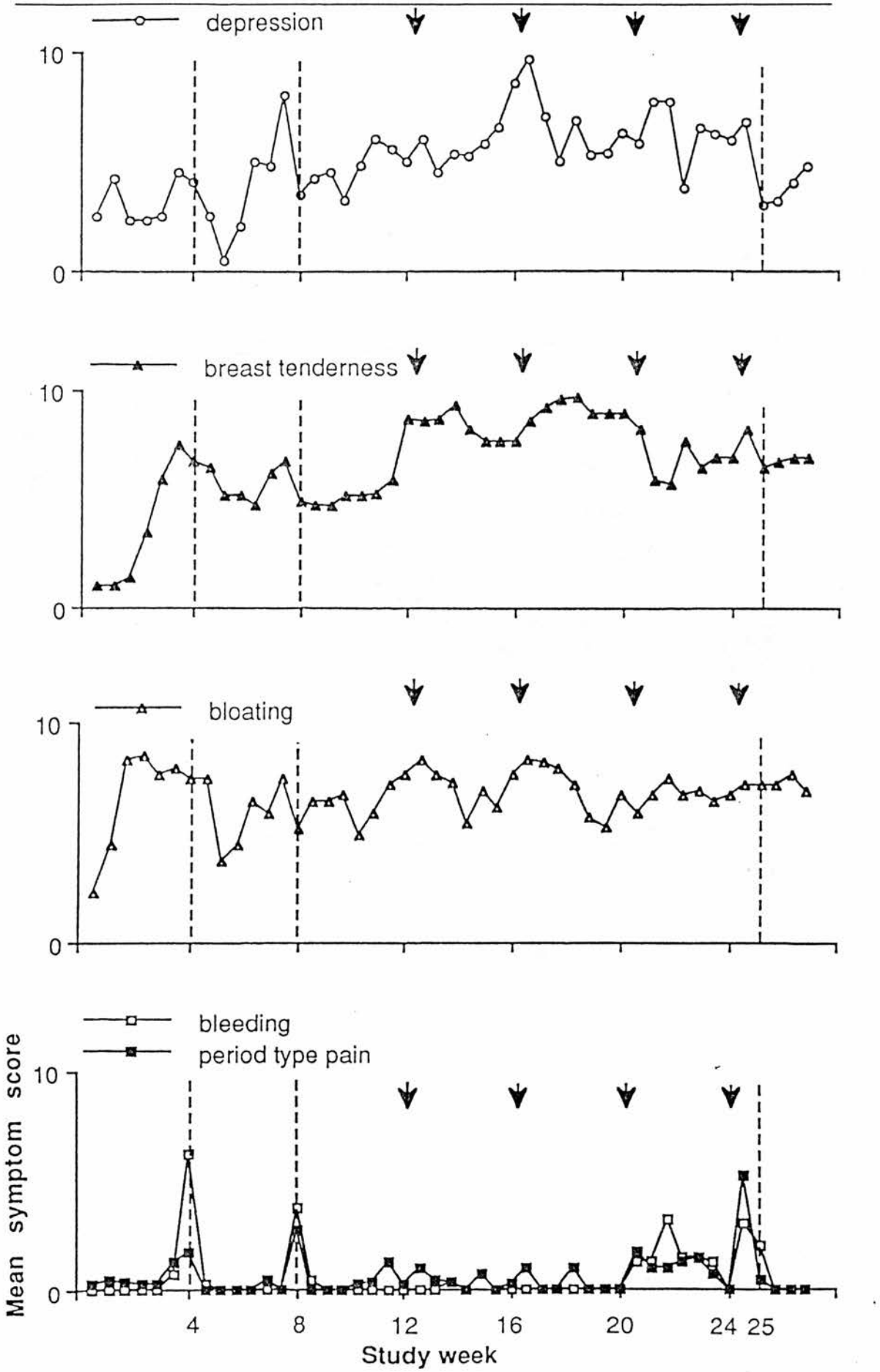

Figure 6.14 Symptom subgroup 1. Profiles of selected mood and physical variables for continuous group member B4. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

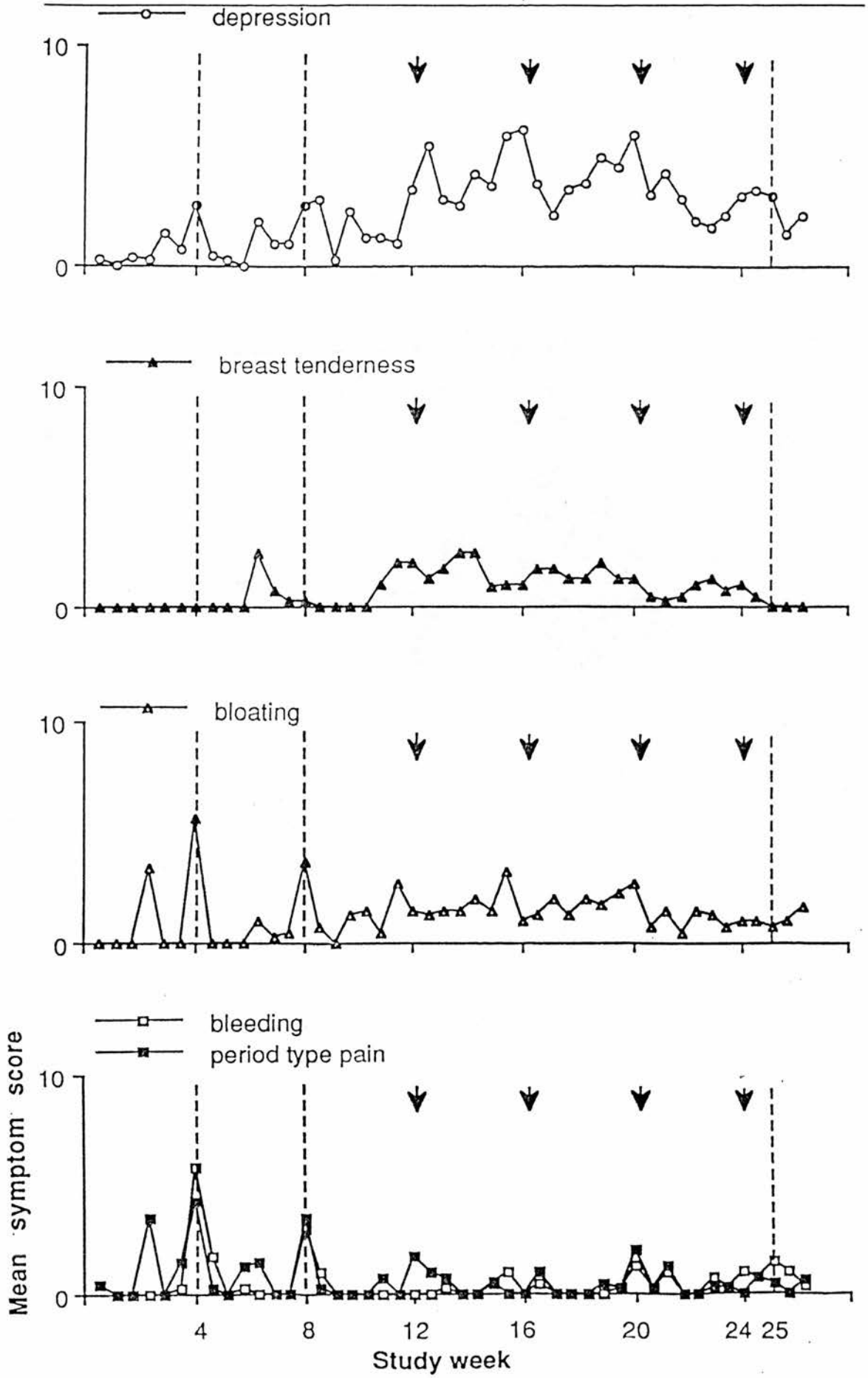

Figure 6.15 Symptom subgroup 1. Profiles of selected mood and physical variables for continuous group member B12. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

bloating, and period pain also worsened and became chronic over the long cycle. Two women eventually gained relief from breast tenderness at the time of the final dummy pill withdrawal bleed in week 25. The third woman whose breast tenderness remains high, was already taking Marvelon when she entered the study, so this effect seems to be attributable to constant steroid administration rather than the formulation *per se.* Bloating does not return to basal levels for any of the three by the end of the study. Period pain does not show the same chronic elevation of the other two symptoms, but tends to become more frequent as the cycle progresses. Although it always occurs with bleeding whether this is scheduled or breakthrough, it also occurs at other, random times. Pain is resolved by the end of the study for the two women whose week 25 bleed was complete, and for the third who was still bleeding, it was waning.

Although the predominant effect in this subgroup seems to be chronic sympotmatology, there is also evidence of persistent cyclicity. A7 and B12 seem to experience an exacerbation of depression and bloating around the times when withdrawal bleeds would have occurred in weeks 12, 16, and 20. The effect is more marked for B12. B4 also has an oscillatory pattern superimposed on a raised baseline of breast tenderness and bloating, but the *period* seems to be greater than four weeks.

A7 also had more migraine headaches during the study which appeared at regular 5 to 6 week intervals[5]. She noted that before starting on the study pill she had infrequent migraines, perhaps once a year. Within two months on Marvelon she had a migraine (week 8), and had three further attacks in weeks 13/14, 20 and 25 (see Figure 6.13). She felt that these headaches were more profound and lasted longer than those in her previous experience. These were not consistently withdrawal headaches as two of the four occurred during active pill taking. Before the study she was taking Mercilon which is identical to Marvelon except that it contains 10μg less EE each day. All three women in this subgroup reported that they usually had some PMS-type experience. A7 reported mild cyclicity, while B4 and B12 reported marked PMS.

B) Symptom subgroup two. The second group of three women, which includes A1, A3, and C8, is in some respects similar to the first. (See Figures 6.16 to 6.18) Their negative mood, particularly irritability either remains apparently cyclical (A1), or actually improves[6]. Breast tenderness and bloating, however, become more severe and

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5
Her experience is similar to that of PMS patient 8846. See figure 5.05.

6
Volunteer A1 was going through a difficult relationship break-up during the study, which seems to be markedly reflected in her depression scores, but not irritability. The other two women had minimal tension/depression.

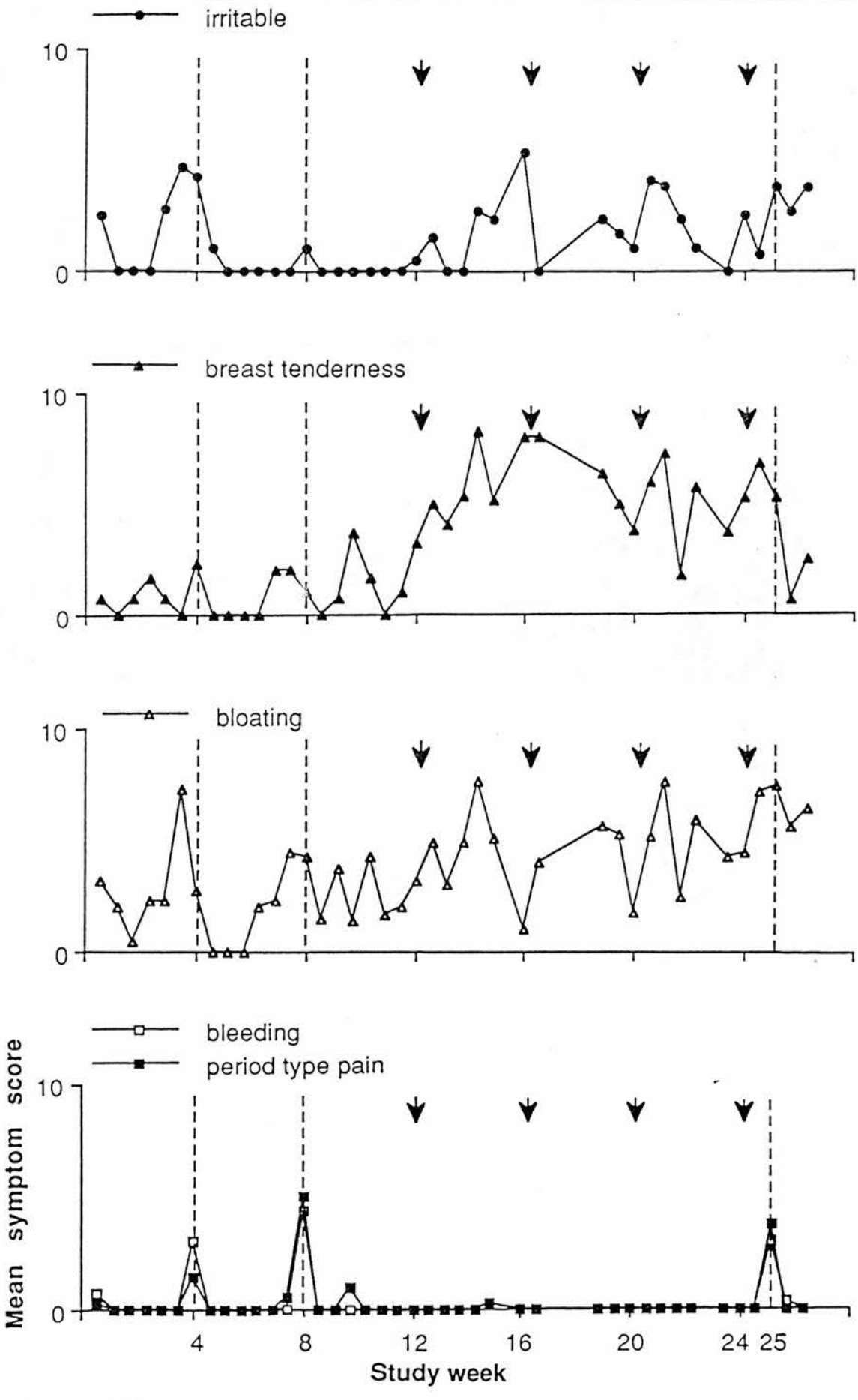

Figure 6.16 Symptom subgroup 2. Profiles of selected mood and physical variables for continuous group member A1 in. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

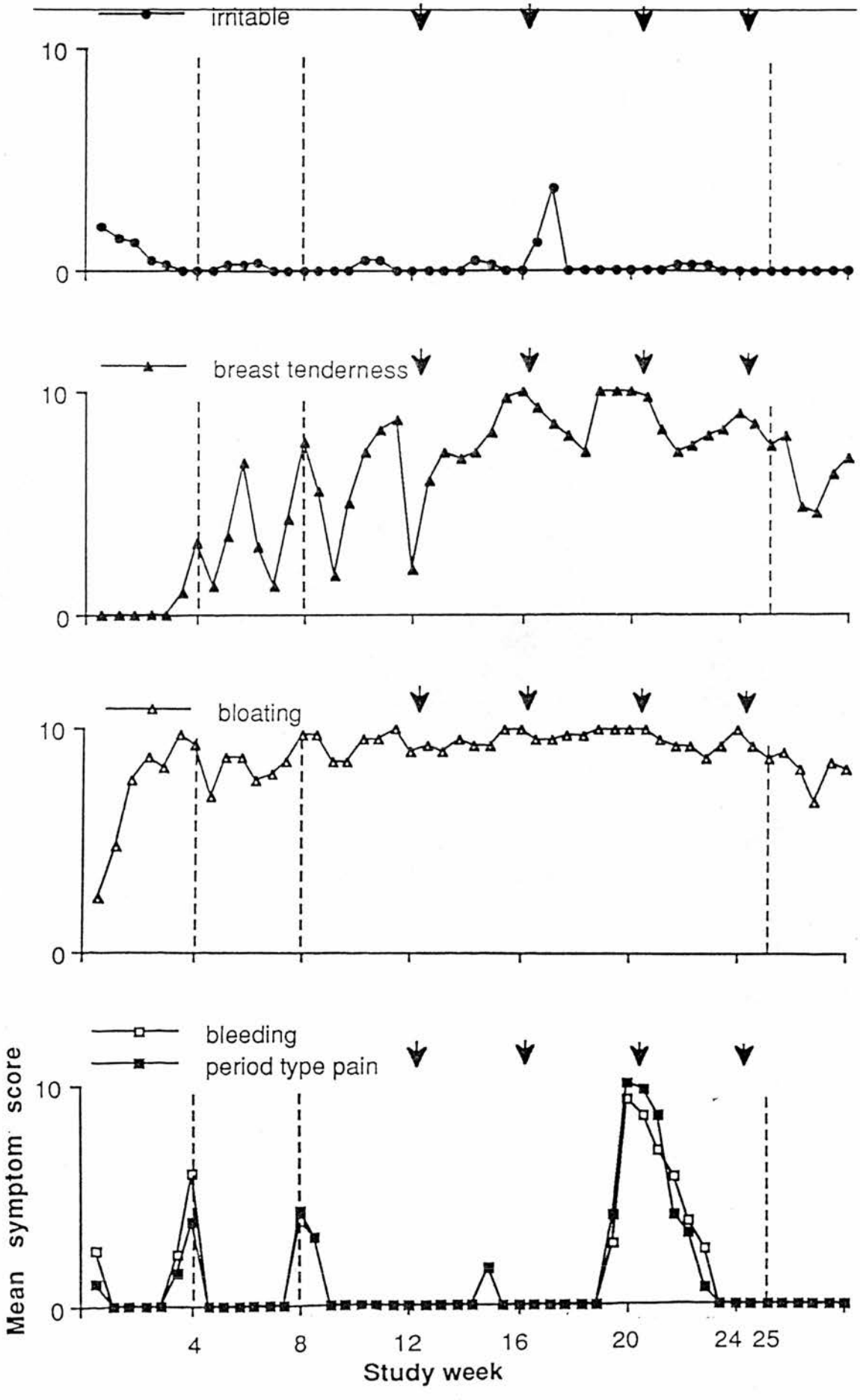

Figure 6.17 Symptom subgroup 2. Profiles of selected mood and physical variables for continuous group member A3. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

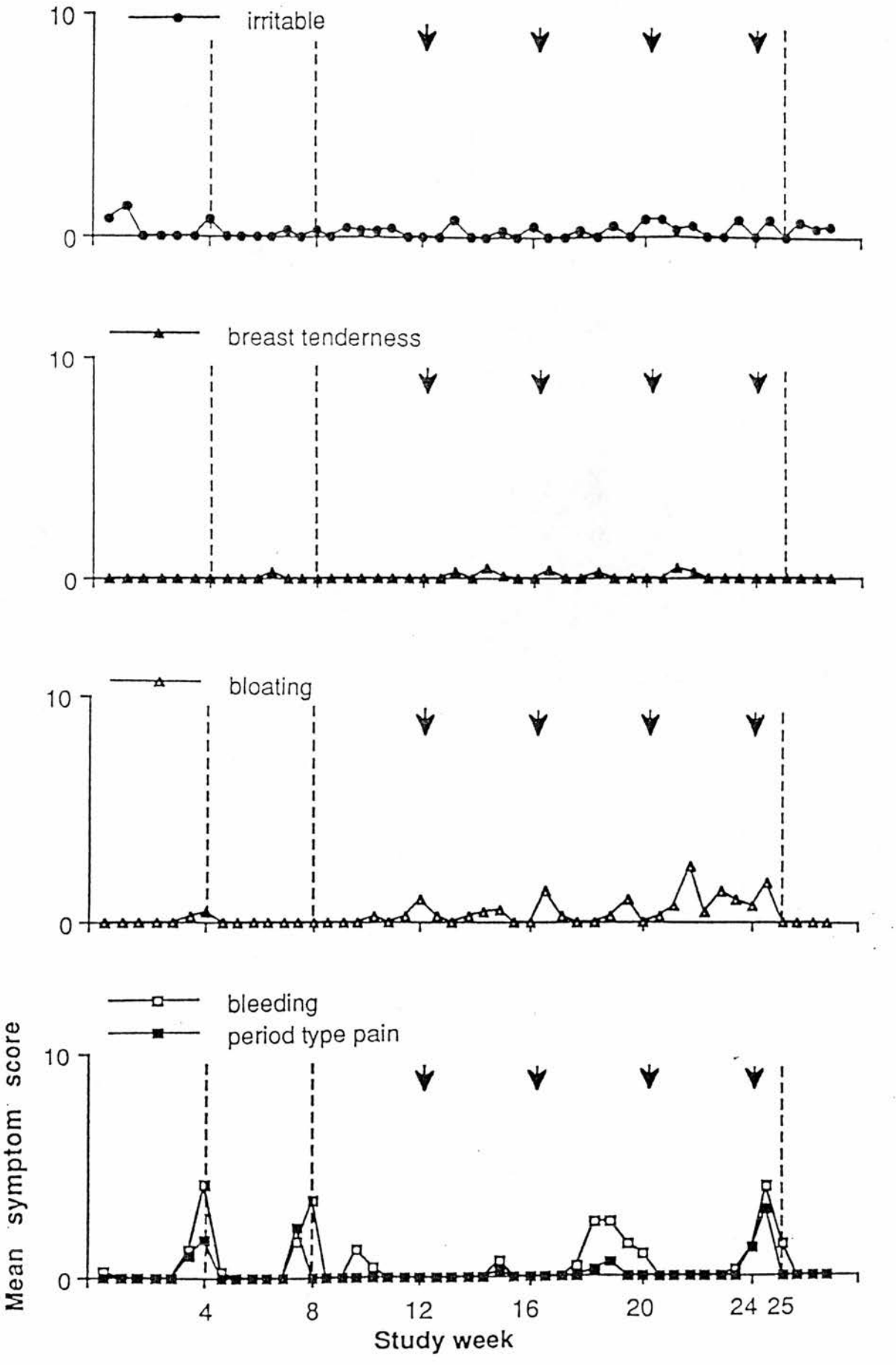

Figure 6.18 Symptom subgroup 2. Profiles of selected mood and physical variables for continuous group member C8. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

more variable after the baseline, during the extended cycle. There is some suggestion that while these symptoms are generally elevated they show exacerbation at the time of would-be bleeds at roughly monthly intervals, viz- breast tenderness for A3 and bloating for C8. The Marvelon taker in this group (A3) shows very similar patterns of breast tenderness and bloating to the Marvelon taker in group one (B4). The profiles of period pain in this group are distinct from the previous group. Pain seems predominantly to occur at the time of bleeding, whether scheduled or breakthrough, but not at other times.

The severity of mood symptoms in this subgroup is consistent with the women's retrospective report of PMS-type changes. A1, who showed the most substantial mood change in her diaries reported having marked cyclical changes at the beginning of the study. A3 and C8, on the other hand, both indicated that they only ever experienced physical changes. Their retrospective report is confirmed by the almost complete absence of moods in their prospective ratings.

C) Symptom subgroup three. The third group of women, including A5, B3, and C3, are distinct from the previous two because they record a resolution of negative moods as a result of the prolonged cycle. This effect is particularly marked for irritability. (See Figures 6.19 to 6.21) One woman, B3, consistently reported during the study that her mood was improved by prolonged pill taking, however, she actually shows some worsening of mood early in the manipulated cycle[7]. While no one in this group was an established Marvelon taker, B3 had been taking Mercilon. All three of these women reported experiencing PMS prior to the study, marked for A5 and B3, and mild for C3, but none showed clear evidence of cyclicity in the two baseline cycles.

A5 who showed the most marked mood change in the baseline had been so distressed by her PMS symptoms when she first entered the study that it almost caused her relationship to break down and her to discontinue the study. She stopped taking the pill for five days in the first control cycle. Instead of dropping-out, she was encouraged to start the pill again, and to re-start the study the following month, thus her first control cycle is actually her second month on encapsulated Marvelon. So the absence of mood change in her second (actually third) cycle may demonstrate that she had already

7
This corresponds to a time when she was having physiotherapy on her Achilles tendons which prevented her from exercising, and was preparing for her up-coming wedding, both of which affected her mood.

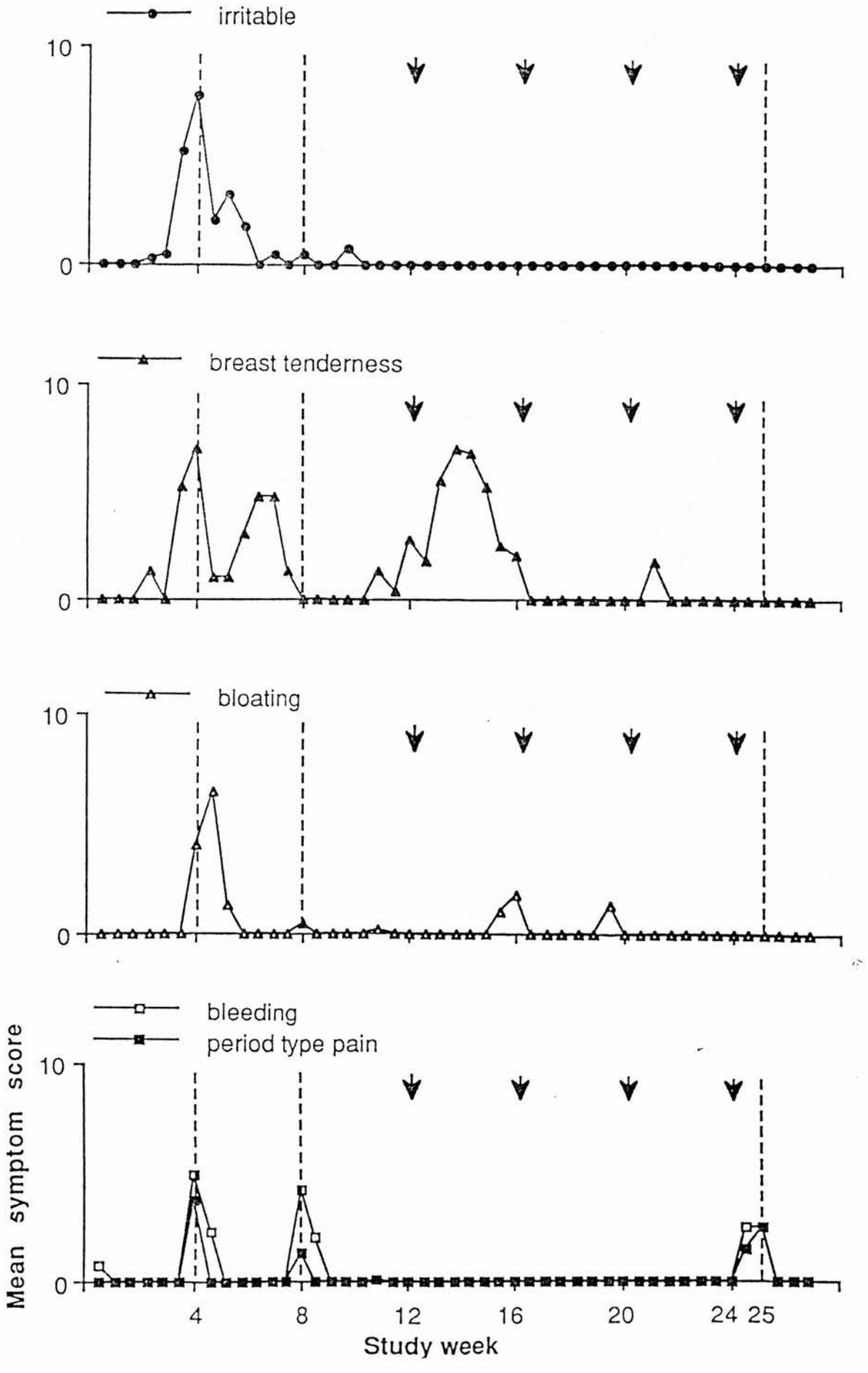

Figure 6.19 Symptom subgroup 3. Profiles of selected mood and physical variables for continuous group member A5. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

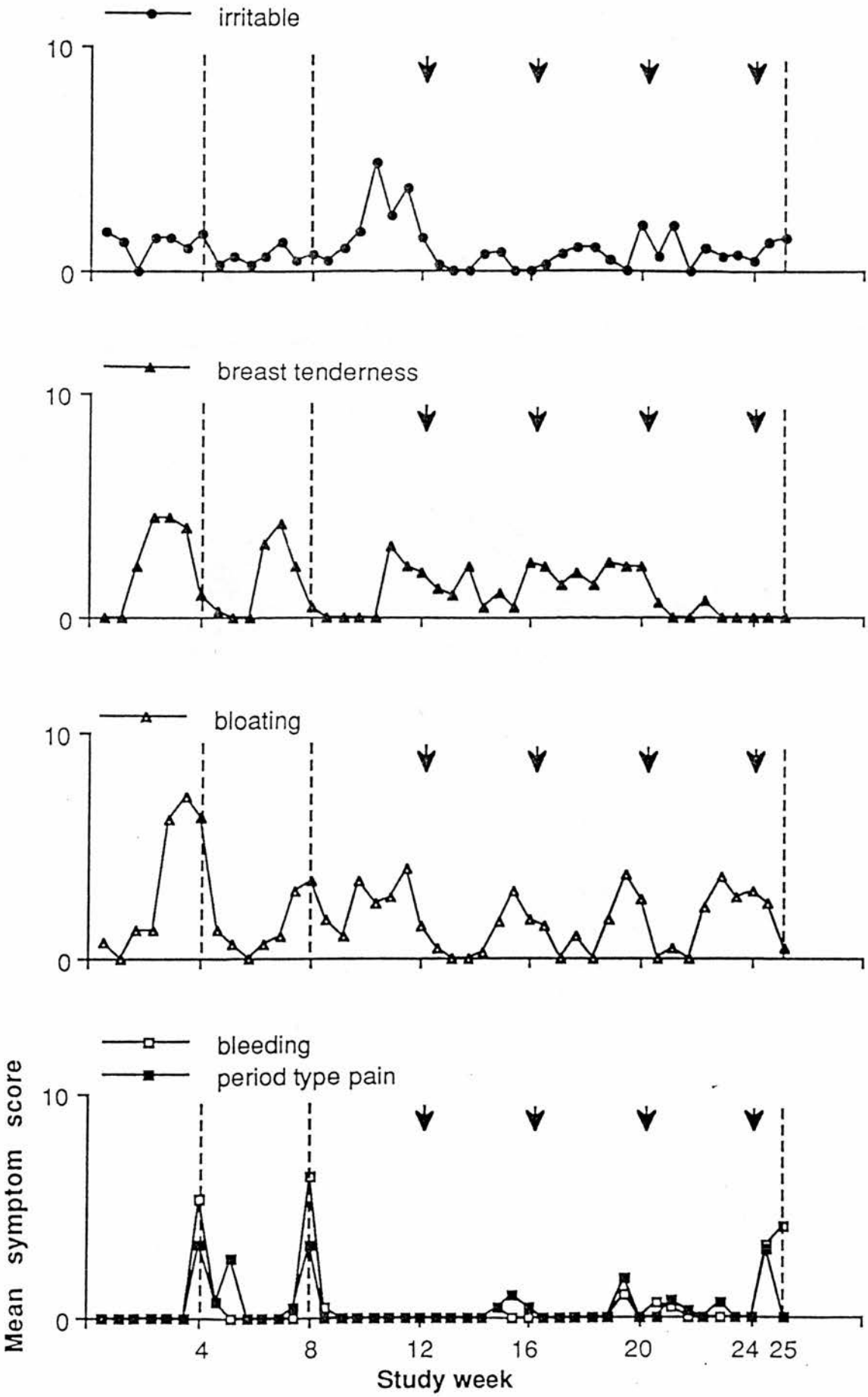

Figure 6.20 Symptom subgroup 3. Profiles of selected mood and physical variables for continuous group member B3. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

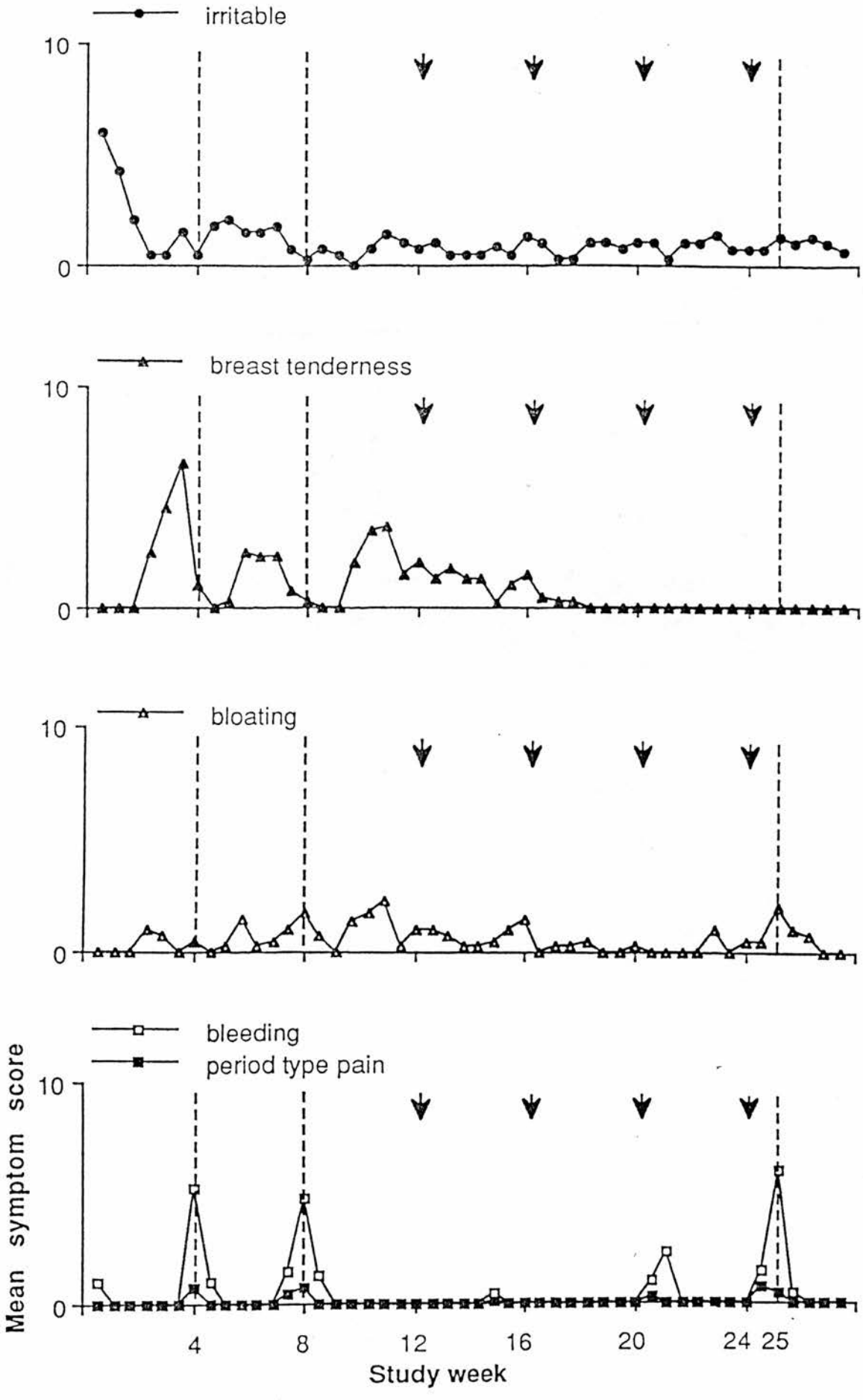

Figure 6.21 Symptom subgroup 3. Profiles of selected mood and physical variables for continuous group member C3. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

adjusted to the Marvelon, and that it was contributing to her improved mood.

The physical symptoms were consistent across all the women. Initially, all three women showed chronic breast tenderness during the extended cycle at levels similar to those seen during the baseline. Unlike the previous six women whose breast tenderness continued until the end of the extended cycle, breast tenderness resolved in these women before the end of the long cycle, prior to any change in the exogenous steroid environment. It lasted longest in B3, but no woman had any breast tenderness after study week 23. Bloating also continued in the long cycle, again at similar or slightly reduced levels to the baseline. Yet instead of becoming chronic, bloating continued to oscillate at approximately monthly intervals with peak levels typically occurring at the times of would-be bleeds. The effect is most marked for B3. Period pain was confined predominantly to the times of scheduled and breakthrough bleeds which were uncommon in this subgroup.

D) Symptom subgroup four. The final group of three women, which includes A4, A11, and B8 are distinctive because all of their symptoms seem to show a degree of sustained oscillation from the baseline through the extended cycle. Their profiles are shown in Figures 6.22 to 6.24.

This group includes the woman, A11, who had to be switched from the control group into the continuous group, late in the study. She was experiencing withdrawal migraine headaches during dummy pill weeks. Rather than loose her to the investigation, she was re-allocated single-blindly to the continuous group. While she was undergoing the conventional four week control cycles she had migraines during each withdrawal bleeding week (4, 8 and 12). She had experienced headaches during bleeding while on Brevinor, but they were less severe and shorter. Her pill sequence was adjusted so that she would have no more dummy pill weeks until week 25. Thus she entered the continuous group after three, rather than two, baseline cycles, and only took active pills continuously for 12, rather than 16 weeks. She had no further migraines until dummy pill week 25, when she had a less severe migraine than she had had previously. This woman's migraines were alleviated by extended pill taking, while A7, described in subgroup one, had the opposite experience.

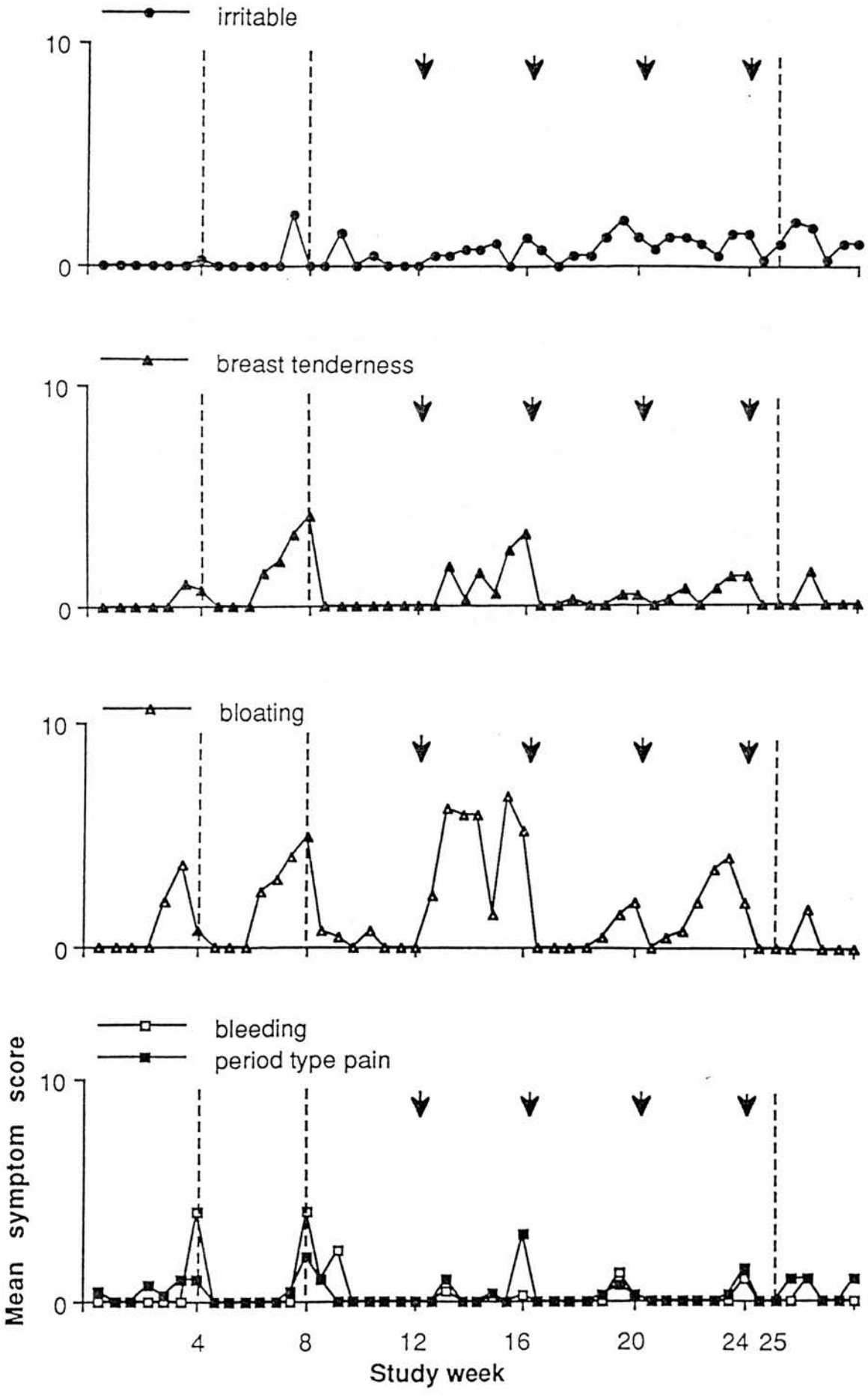

Figure 6.22 Symptom subgroup 4. Profiles of selected mood and physical variables for continuous group member A4. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

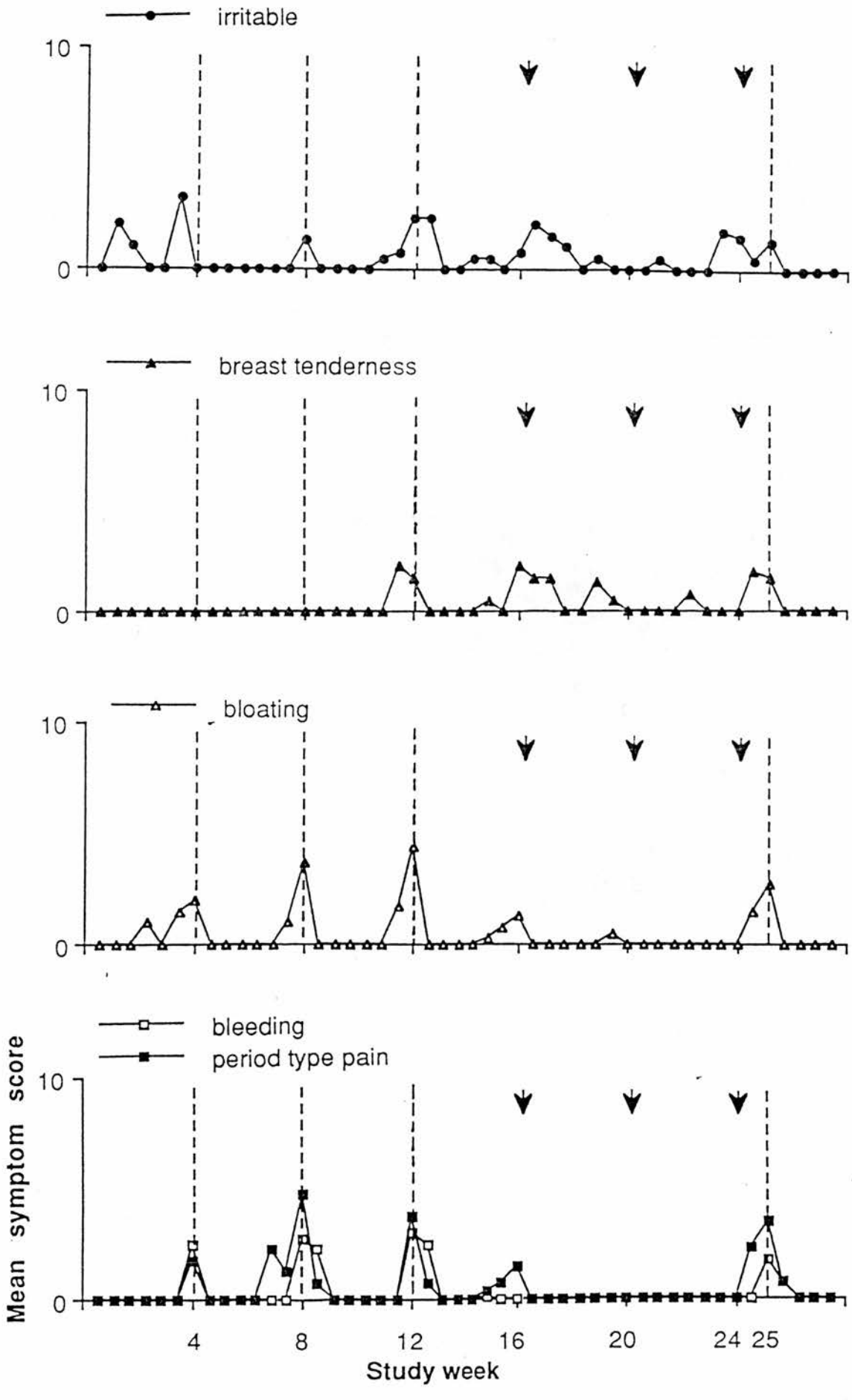

Figure 6.23 Symptom subgroup 4. Profiles of selected mood and physical variables for continuous group member A11. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

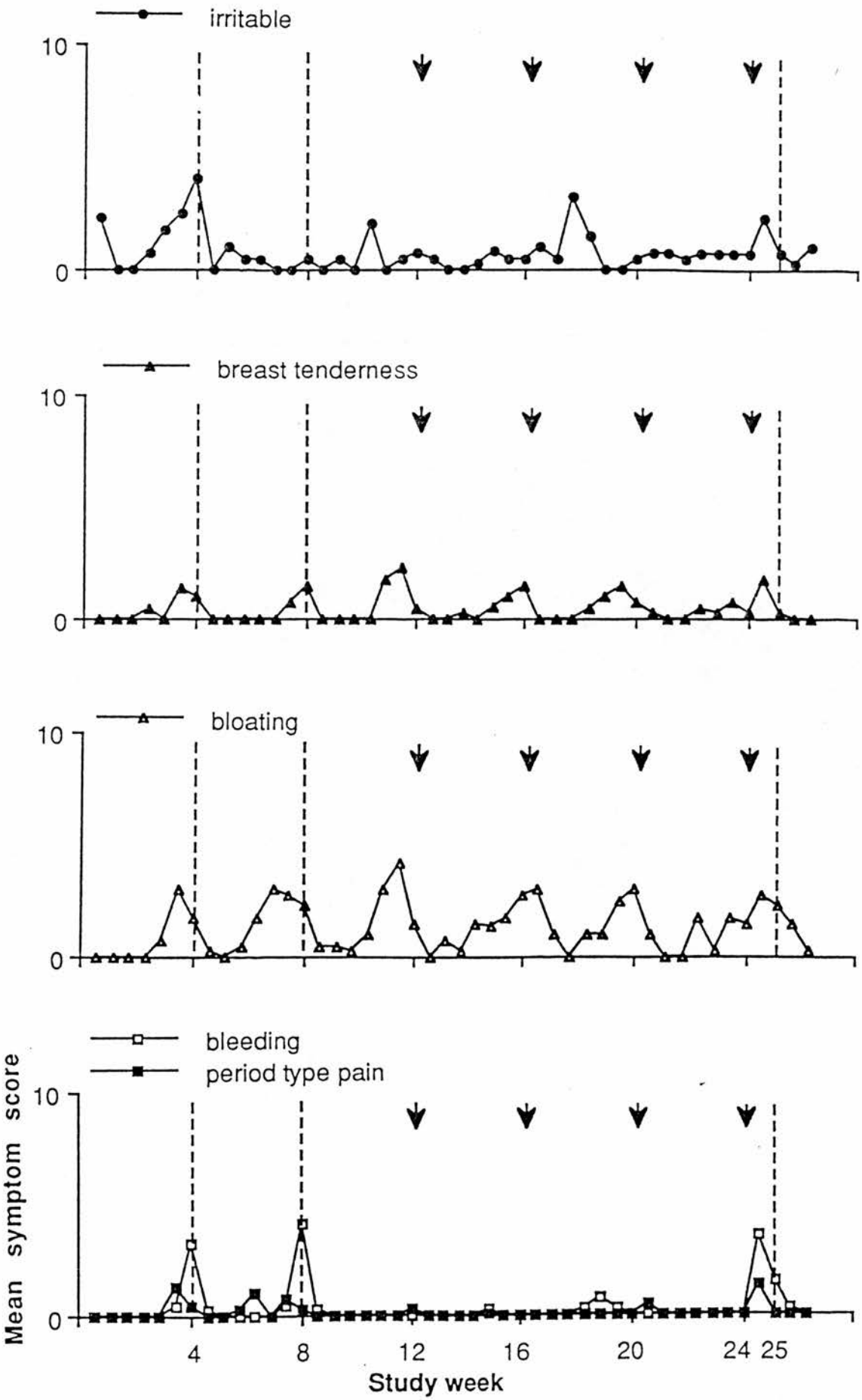

Figure 6.24 Symptom subgroup 4. Profiles of selected mood and physical variables for continuous group member B8. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

The pattern of symptoms in this group is, as previously, not as clear for moods as for physical symptoms. There is roughly monthly oscillation in irritability in all three women, which is most marked during the three months of continuous pills for A11. The pattern of breast tenderness is quite similar across the women. B8 shows the most consistent pattern with breast tenderness rising to a peak just before the would-be bleeds in weeks 12, 16, 20, and 24. Bloating also shows a marked and regular oscillation, again with a very clear pattern for B8, but quite pronounced oscillation for A4 and A11. Finally period pain occurs predominantly at the times of scheduled or breakthrough bleeds, but does show a slight tendency to occur at approximately the times of would-be bleeds, though it is not marked in any of the three women.

These three women all gave different retrospective accounts of PMS experience. A4 believed she had only slight changes in moods and physical symptoms. A11 reported having mild PMS-type changes, and B8 noted marked cyclicity.

6.5.8.3 The severity and timing/cyclicity of selected diary variables in the phase shifted group

The gross difference in the severity of mood and physical scores between the baseline and manipulation phase was determined as before using t-tests. Like the continuous group, all the volunteers in this group should have had significantly less bleeding, yet only 1 out of 15 recorded a reduction in the second four months Again this is probably due to breakthrough bleeding. Women also continued to experience the same mean daily amount of period pain while having fewer scheduled bleeds. The distribution of change in mood symptoms is virtually identical to that for the continuous group. And the reasons for this may be similar. Not quite so many women in this group had more breast tenderness, but many were more bloated.

Table 6.12 Phase Shifted Group: Number of women showing significant difference ($p<0.05$) in mean diary score from baseline to "manipulation" on Student t-test

Direction of Change	Bleeding	Period type pain	Irritability or Anger	Depression or Tension	Breast tenderness	Bloating
no change	14	12	10	8	10	5
more	-	1	1	5	2	6
less	1	2	4	2	3	4

This group was similar to the other study groups in that the physical variables showed a much clearer pattern than the mood variables. Fifteen women completed the study in this group; the diary data for two was of limited interest because they were virtually asymptomatic. For the thirteen women remaining one pattern of symptom timing predominated. In 8 women the pattern of variation over time in breast tenderness, bloating and period pain was sufficiently clear and consistent to merit producing the mean symptom profiles, which are shown in Figure 6.25.

In the majority of these women the three symptoms occurred before or during withdrawal bleeding in the two baseline cycles. During the phase shifted cycle, however, physical symptoms showed a tendency to begin early, with significant symptoms occurring just before or during the would-be bleeding time in week 12. Breast tenderness peaked in week 11 and was falling during week 12, but it began to rise again in the absence of a bleed. It only fell as a result of the withdrawal bleed in week 14, reaching the baseline in the next week. Almost immediately it began to increase once again, but this time the peak in week 17 was closer to the actual bleed in week 18. By the third bleed after the phase-shift the pattern looked very similar to the baseline. In the next cycle the pattern is the same, with breast tenderness falling in week 26 in spite of the fact that there is no withdrawal bleed in this week.

The pattern is similar for bloating except instead of regressing spontaneously in week 12 it continues to be raised until the withdrawal in week 14. The mean does not return to baseline levels immediately after this bleed but continues irratically until it peaks in

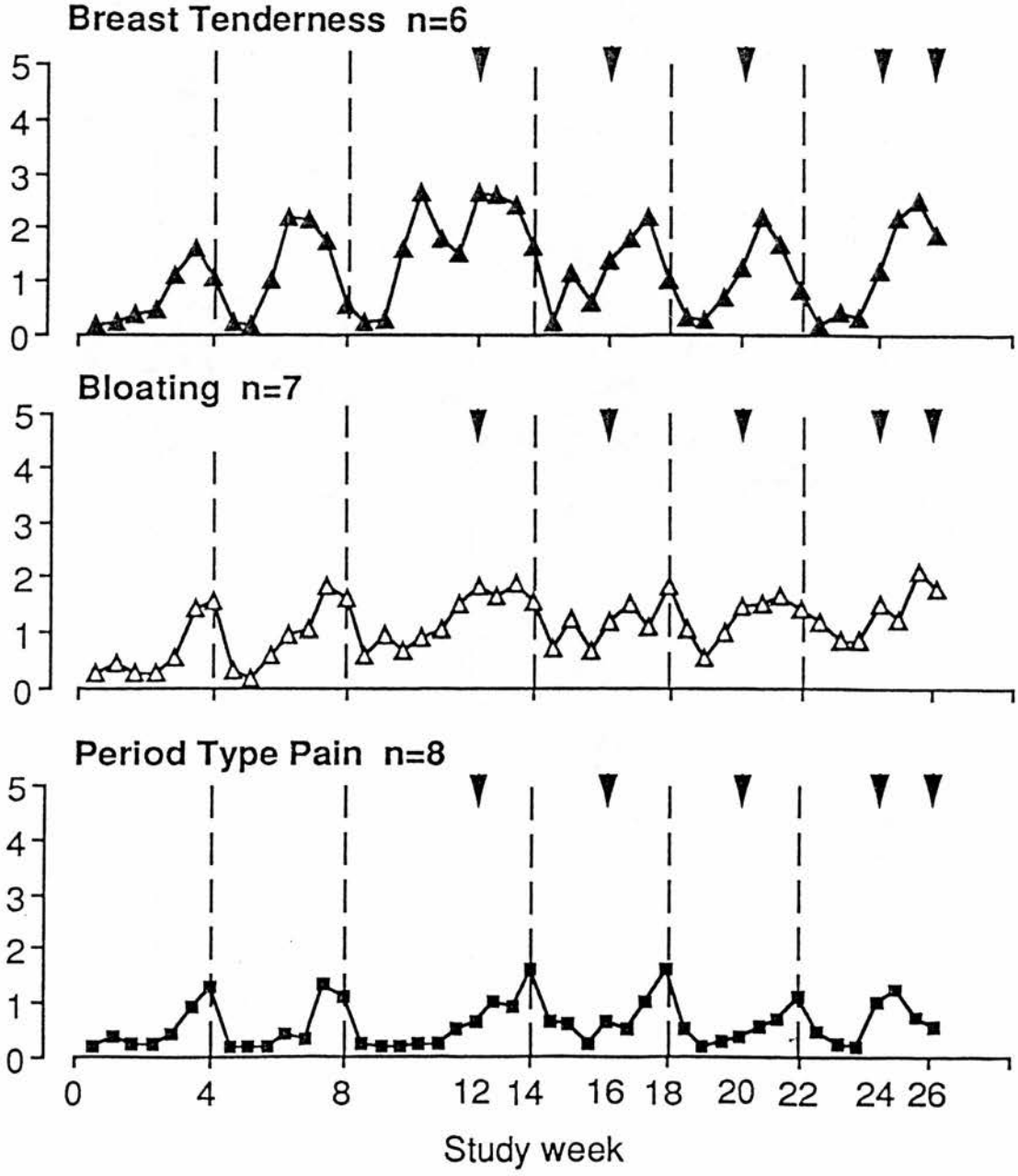

Figure 6.25 Mean profiles of three typical physical symptoms from 8 women in the phase shifted group. Dotted lines indicate the position of pill free intervals. Closed arrows indicate the position of "would-be" withdrawal bleeds.

the next withdrawal week, 18. The profile in the third "cycle" looks more like the baseline than the previous one, and once again bloating increases and peaks just before the newly entrained would-be bleed in week 26. It would seem that the phase shift had a greater disoganizing effect on bloating than it did on breast tenderness, nevertheless, there does seem to be a gradual re-entrainment to the new cycle after the transient disruption.

Period pain is more closely tied to the immediate pre-bleeding and bleeding phases during the baseline than the other two symptoms. The response of period pain to the phase change is much the same, with a rise beginning in week 11 that is sustained until week 14, followed by a fairly chaotic cycle. The third cycle after the shifted one is like the baseline, and pain appears in week 24, peaks in 25, and is declining in week 26.

It was serendipitous that the ordinary packet of Marvelon given at the end of the study produced a cycle that lasted seven weeks. This was in fact longer than the originally planned phase-shift. Because the majority of women continued to fill in diaries for a few weeks into the packet of Marvelon, there are data for the would-be bleed in week 26. It appears that after the first disruption, the physical symptoms have gradually re-entrained to the new cycle timing. The rise of symptoms in week 26, when there is no steroid withdrawal, reflects the effectiveness of the re-entrainment.

There is unfortunately no similarly clear picture of disruption followed by re-entrainment for mood variables. None of the mood scales for the women in this group showed any marked cyclicity, although 5 women reported mild and 6 marked cyclical change retrospectively. The worst symptoms which women reported retospectively do tend to agree with those scored most severely in the diaries. Notably, the 8 women who showed marked cyclicity of physical symptoms had generally reported these retrospectively. Equally, without having based the decision about how to group women's diary patterns on a prior knowledge of retrospective PMS reporting, the groups do follow these lines. The 8 women with cyclicity in all of their physical symptoms all reported either mild or marked PMS retrospectively. Three women were not included in the mean, but did report PMS experience. The one who noted mild PMS was free of physical symptoms. The two who noted marked PMS (A15 and B10) did show cyclical bloating, and A15 may also have had the prevailing pattern of breast tenderness and period pain.[8]

8

It is important to note that within the sub-group of eight women there were equal numbers with and without breakthrough bleeding. The sub-group also includes two women who had very substantial oestrone peaks, yet five for whom they were very slight or only moderate. Thus there does not seem to be any consistent relationship between bleeding patterns or residual ovarian oestrogen and the pattern of physical symptoms seen.

6.5.9 The Influence of Psychometric Variables on Response to Cycle Manipulation

The distribution of the EPI scale scores relative to the published total population norms are summarized in Figure 6.26. It is acknowledged that women tend to score higher than men on neuroticism, and lower on extroversion (Eysenck & Eysenck, 1964). In this sample however, 78% of scores fall within one standard deviation of the population mean for neuroticism. This population also shows a strong tendency to greater extroversion, with 83% of scores at or above the mean. The lie scores were also relatively conservative. Only 4 women had lie scores >/= 4, with the maximum at 6. Five is taken to be the maximum score at which the test can be reliably accepted (Eysenck & Eysenck, 1964).

Internal versus Powerful Others LOC is shown in Figure 6.27, and versus Chance LOC in Figure 6.28. The majority of women scored within the normal range for Internal LOC (81% within 1SD), yet only 39% did so for Powerful Others and 61% for Chance. All of the outliers scored low for Powerful Others, and all but one high for Chance. The indication is that for this sample chance is a more meaningful external determinant of health than are people like doctors, nurses, etc..

Based on the cut-off scores described in Beck et al. (1988), 75% of this sample report no or minimal depression. And in the remaining 25% only mild to moderate depression is indicated. No one was therefore excluded from the study due to depressed mood.[9] The distribution of Beck scores across groups is summarized in Figure 6.29.

This is difficult to assess because A15 had missing data during both of the phase shifts.

[9] The psychometric test scores of the five of the women who dropped out of the study late were calculated and compared with the other study groups. The means scores for the drop outs were similar to the continuing groups except for depression. The drop outs were substantially more depressed. Two women had no depression, while one had a moderate BDI score and two were severely depressed.

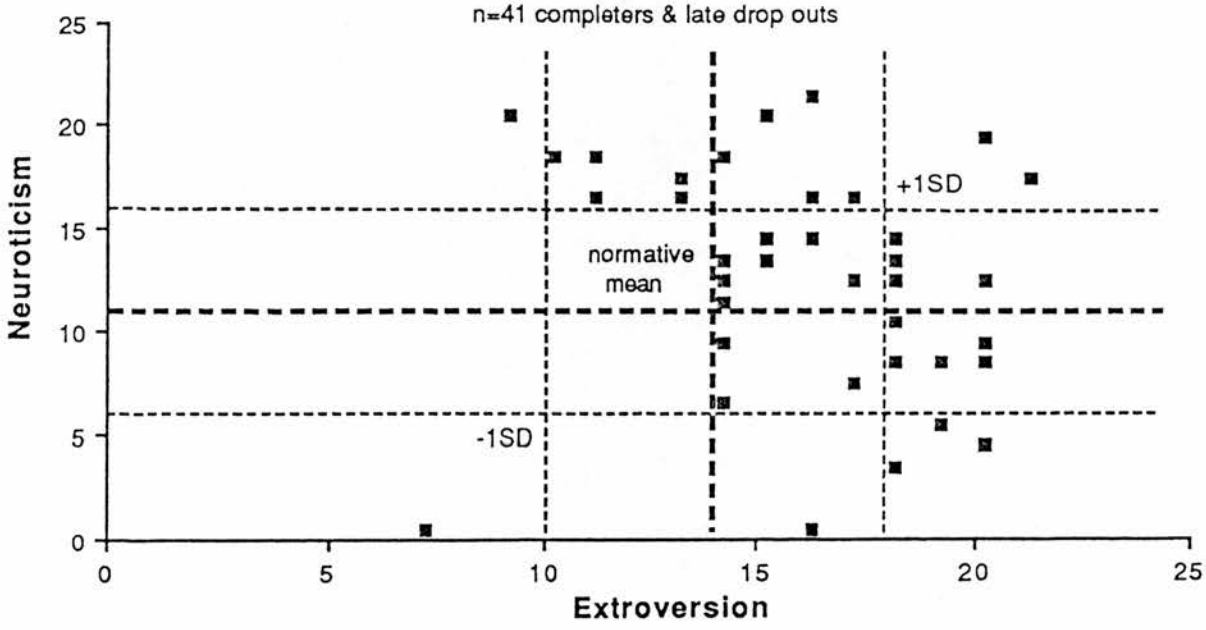

Figure 6.26 Scatter of Eysenck Personality Inventory scores relative to the published population norms. Thick dotted lines indicate population means; thin dotted lines indicate population standard deviations.

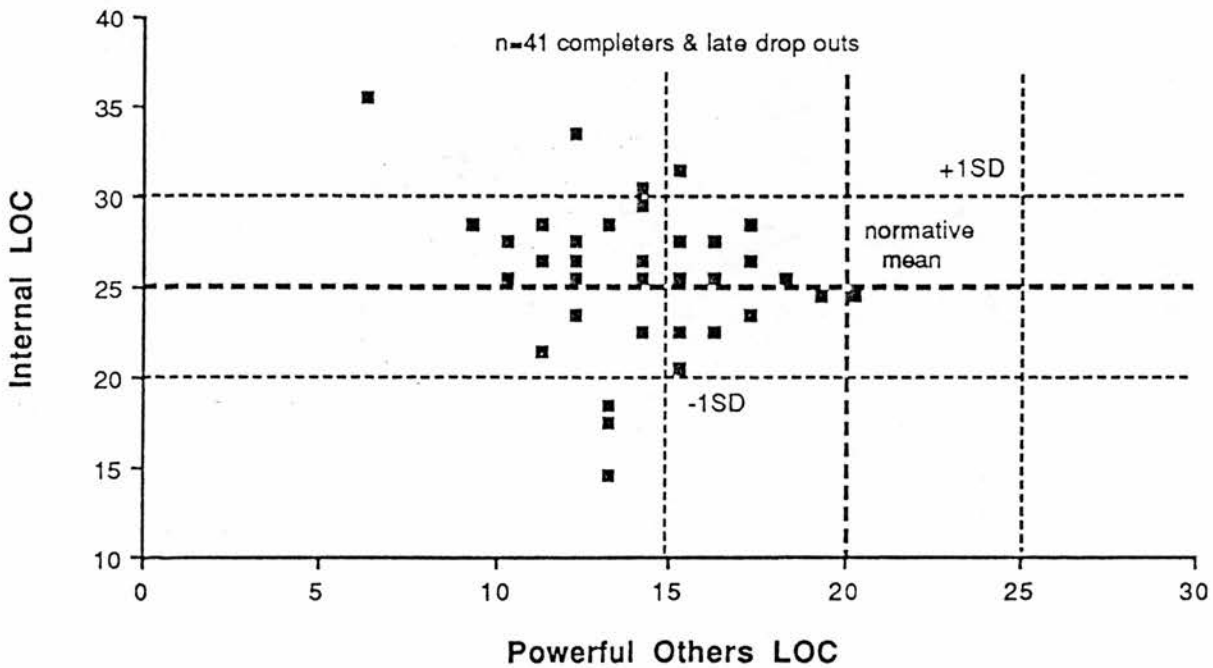

Figure 6.27 Scatter of Internal versus Powerful Others Multidimensional Locus of Control Scores relative to population norms. Thick dotted lines indicate population means; thin dotted lines indicate population standard deviations.

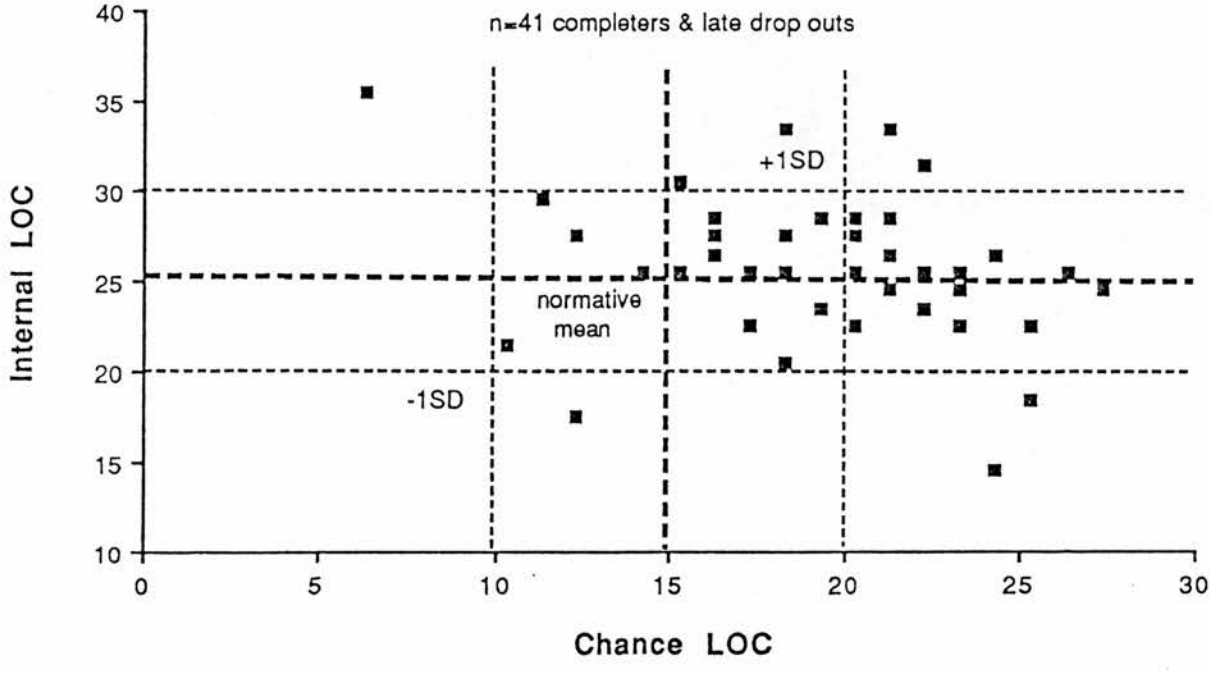

Figure 6.28 Scatter of Internal versus Chance Multidimensional Locus of Control Scores relative to population norms. Thick dotted lines indicate population means; thin dotted lines indicate population standard deviations.

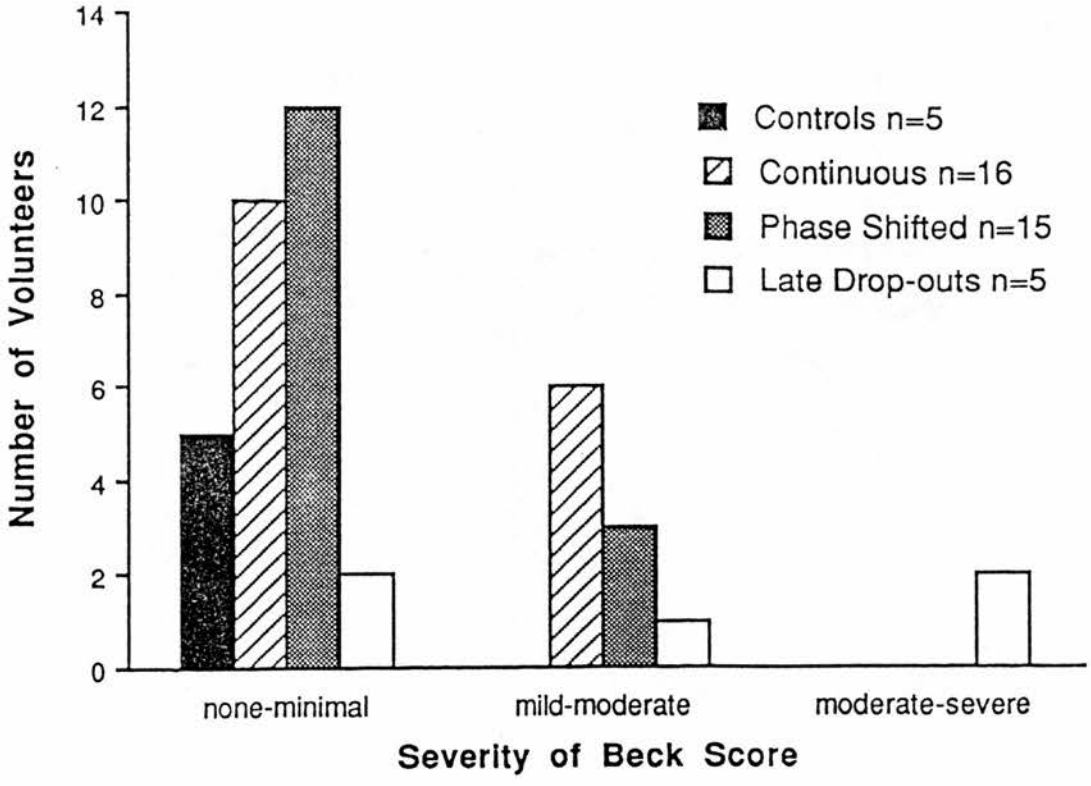

Figure 6.29 Distribution of Beck Depression Inventory scores across the study groups and drop-outs.

Comparisons were made between the three study groups using Student's t-tests and no significant differences were found for Extroversion (Control vs. Continuous t=1.16, p=0.26; Control vs. Phase shifted t=1.13, p=0.27; Continuous vs. Phase shifted t=-0.17, p=0.86) or Neuroticism (Control vs. Continuous t=1.05, p=0.30; Control vs. Phase shifted t=0.91, p=0.37; Continuous vs. Phase shifted t=-0.13, p=0.39). There were also no group differences for Internal (Control vs. Continuous t=-0.68, p=0.50; Control vs. Phase shifted t=-0.99, p=0.33; Continuous vs. Phase shifted t=--0.79, p=0.43) or Chance LOC (Control vs. Continuous t=-0.95, p=0.35; Control vs. Phase shifted t=-0.47, p=0.64; Continuous vs. Phase shifted t=-0.42, p=0.67). In keeping with the general trend in the data towards low Powerful Others LOC, the phase shifted group had significantly lower PLOC than the continuous group (t=3.31, p<0.01). The three study groups did not differ in mean BDI score, yet the drop-outs had significantly higher Beck scores than the phase shifted group (t=-2.35, p<0.05) and non significantly higher scores than the control and continuous groups.

Further comparisons were made between "symptomatic" subgroups to discover whether test results predicted study response. Within groups correlations were also sought between test scores. Tests on subgroups were not made for the controls as there were too few of them. For the continuous group, subgroups 1 and 4 (mood+) were combined and compared with subgroups 2 and 3 (mood-). The resulting groups reflect the presence or absence of notable diary ratings for mood respectively. The mood+ group had chronic/cyclic moods and physical changes, while the mood- group had irregular or resolved moods and chronic/cyclic physical changes. There were no significant differences for these mood groups on neuroticism, LOC, or depression, nor did any of the tests correlate significantly with one another within groups.

The phase shifted group was divided into two subgroups based on the presence of cyclicity in the three physical variables. The 8 women who were included in the means for physical variables above constitute the "cyclical" group and the remaining 7 women who did not show a consistent pattern or were asymptomatic are "non-cyclical". There was no significant difference between the two groups for LOC or depression. However, the women in the cyclical group were significantly more neurotic than the non-cyclical group [t=4.24, p<0.00, mean: 15.3 (4.1) vs. 6.6 (3.8)]. While there was no significant correlation between Beck scores and neuroticism or LOC for the cyclical and non-cyclical groups, neuroticism was significantly positively correlated with

Chance LOC for the cyclcial women ($r=0.79$, $p<0.05$). ILOC and PLOC did not differ between subgroups.

When all women in the phase shifted group were taken together this correlation between neuroticism and CLOC was upheld ($r=0.64$, $p<0.01$). There was also a significant inverse relationship between neuroticism and ILOC in the whole group ($r=-0.59$, $p<0.05$). There was no significant relationship with PLOC.

There was a near significant relationship between neuroticism and Beck scores ($r=0.50$, $p=0.056$) in the phase shifted group. Neuroticism was significantly correlated with depression in the Continuous group as a whole ($r=0.53$, $p<0.05$). There was no relationship between neuroticism and LOC in this group, however, the BDI correlated with PLOC ($r=0.57$, $p<0.05$).

Because PMS is known to be related to neuroticism, the relationship between retrospectively reported PMS status and N scores was examined. Over the whole sample 15 women (42%) reported marked PMS, 11 mild (31%), and 10 none at all or physical symptoms only (27%). Women with N scores of 16 or higher were considered to have high neuroticism. Twelve women (33%) had high N scores and their distribution by PMS status was relatively even: 6/15 marked (40%), 3/11 mild (27%), 3/10 none/physical only (30%). Thus self-reported PMS status did not seem to relate to a propensity to score highly on the EPI for neuroticism. And as demonstrated above there was only a limited tendency for high N scores to be related to prospective symptom reporting (phase shifted "cyclical" only).

6.5.10 The Acceptability of Manipulated Pill Cycles to Women

A final consideration of this chapter must be the acceptability of cycle manipulations to women. It is clear that the manipulations influence bleeding experience and seem to affect well being. The acceptability of the regimes were assessed in two ways: informally during monitoring interviews, and formally by open questions during the final interview, and on the study assessment form. These included: What did you dislike about taking part in the study? Did you dislike not knowing when you were going to bleed? Did you have any irregular bleeding? How did you feel about this? Were you worried that you might become pregnant? What was positive for you about

taking part in the study? Would you take part in a similar study again? Would you recommend it to a friend?

These questions elicited a variety of statements from women that reflect certain recurring themes. These themes are largely consistent with the ideas expressed in previous chapters of this thesis, notably that regular vaginal bleeding is taken as an indication of non-pregnancy, fertility, and good health. Women perceive a normal range for acceptable bleeding experience, and scrutinize and question any experience which deviates from it. This study was designed to produce just such deviations, albeit in a controlled and supportive environment.

A) Fear of pregnancy. About half of the volunteers expressed a specific fear that they might be pregnant: 0/5 controls, 7/16 continuous, 8/15 phase shifted. For the majority the first "missed period" in week 12 produced considerable anxiety. A number of women telephoned for reassurance at the time that this bleed was expected, and most women were eager to know the result of their pregnancy test in this month. Pregnancy fear was common in spite of the fact that it had been repeatedly emphasized that the study might involve longer than normal cycles. Of those who had been concerned, about half commented that their fear was transient. They were no longer concerned after the first missed bleed in the two manipulated groups, and after the first few months with regular cycles in the control group. Only one woman indicated that she was increasingly concerned the longer she went without a bleed in the continuous group (A6).

B) Other concerns about irregular bleeding. Amenorrhea was associated with fear of future infertility or adverse health consequences for a few women. Curiously those women with more information, the nurses and the parous women, expressed more anxiety about the absence of bleeds. One nurse (C9) carried out a home pregnancy test. All three parous women were particularly concerned about pregnancy. Two (A5,C4) began to associate food cravings with possible pregnancy, and the third (A3) who was not even sexually active during the study was nevertheless worried[10]. A3 also queried whether or not her "periods" would return after the study. It seemed that the fear of no-bleeding made BTB acceptable, as A3 experienced a 4 week long,

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This apparently irrational fear seems to be connected with the experience of one of her friends who was sterilized then subsequently conceived. This volunteer knew that theoretically she could not be pregnant, yet "theoretically" nor could her friend.

heavy BTB during the extended cycle, but she did not complain about it. Under other circumstances protracted bleeding itself might cause alarm. However, A3 was reassured by it and considering it a "period" said "I just sort of made up for the one that I'd missed". Another nurse (B12) had BTB which she knew could have been a consequence of study manipulations. But because she had never had it before, she began to "get a bit twitched" since she knew medically that irregular bleeding occurs in cancer of the cervix.

Two other women indicated that it was simply the novelty of not bleeding which affected them, saying that it was strange "psychologically". The women in the sample with very high internal LOC, as well as a few others, noted that they disliked not knowing when they were going to bleed, because they disliked not being in control. An additional common reason was social. At least a quarter of women were anxious least they be "caught out" by unsuspected bleeding. There was a fear of "exposure" and being without the equipment for concealment. Therefore, a number of people carried pads and tampons with them at all times. Further, B12 perfered to have regular bleeds so that she could "rationalize things in terms of the cycle".

Women gave several reasons why they did not fear pregnancy, or did not worry about not knowing the planned time of bleeds. First of all, about a quarter of women expressed faith in the technology. Either they felt secure of the pill's efficacy, they relied on the accuracy of the hCG tests, or they were confident of the safety of the study. One woman (C14) simply said that she was "not at all bothered" about the effects of the study on her bleeds. Another (B15) stated "I loved not knowing when I was going to menstruate...every 4 weeks is a drag, even with these tiny little periods on the pill." A10 said that she found it easier to take a pill every day. Many women indicated that they did not worry about the arrival of bleeds because they had symptoms as an early warning. Some women reported mood changes and some physical or both. Pain was a particularly reliable indicator of impending bleeding.

C) Likes and dislikes of the actual experience. Women also commented about their likes and dislikes of the actual experience of amenorrhoea or BTB. About 8 women noted that they liked not having the hassle, inconvenience or disruption associated with monthly bleeds. A7 stated that she "would be delighted to take the pill all the time", and have no further 'periods'. A11 said, "I don't think you need a period every month. It doesn't make them any different. I think 2 times a year would be fine-

3 times a year." Three women (A5, B3, B8) liked not bleeding because they associated it with a lack of PMS-type symptoms. B8 (who did in fact appear to have persistent cyclicty) said, "I really did enjoy not having the periods- it really made a big difference." And B3 was "very disapointed" when she finally did have a bleed.

A few women recorded being aggrevated by BTB. B11 felt that BTB affected her mood because it put her "out of sorts", and A4 found spotting annoying and ill timed. Some women were annoyed when surprise bleeding stained underclothing. C4 did not like BTB at all: "I just feel dirty; I don't like wearing a tampon every day." Several women in the manipulated groups were eager to bleed by the end of the study, not due to pregnancy fear, but to relieve a build-up of symptoms. B9 had bad PMS in the second phase shift, and "never wanted a period so much in [her] life." A1 wanted a period to relieve her substantial bloating and breast tenderness, while C4 felt her 'period' could not be withheld any longer: "Only just holding a period at bay; like a dyke holding this period back."

6.6 Conclusions and Discussion

No single biological phenomenon or substance is able to explain the apparently regular variation in well being that a proportion of women experience in association with the steroid cycle. This chapter has explored the alternative possibility that cyclical change may be the result of a long term endogenous rhythm which becomes entrained to the steroid cycle.

Although this investigation was quite demanding, only 3 out of the original 47 dropped out due to possible effects of the cycle manipulations. The fact that one of these women felt she gained weight, etc. due to the study pill although she was already taking Marvelon when she entered the study implies that some adverse reactions may not have arisen from changes in formulation or cycle length, but constitute false attribution. The age range of volunteers was broad and women were well established on the pill with over 80% having taken it for at least 1 year. Of the 36 women who completed the study, 6 were current Marvelon and 2 Mercilon takers. Almost all women had significant experiences and hassles over the study which might have effected their daily ratings or oestrone levels. These were mainly minor ill health, antibiotic use, and relationship changes.

6.6.1 Breakthrough Bleeding: Endometrial Atrophy or Receptor Fatigue?

In the UK clinical trials of Marvelon (Wiseman, et al., 1984) the incidence of breakthrough bleeding was found to be about 5%, and spotting 7%. During the first 11 weeks of this trial over 27% of volunteers recorded bleeding during active tablet taking, making the frequency of unscheduled bleeding in the baseline months greater than double the UK incidence. There is no obvious explanation for this finding, save that women prone to BTB were more inclined to volunteer to take part, perhaps because they would be less concerned about the potential for the study to disrupt bleeding. Another alternative is that the discrepancy comes from a methodological difference. The participants in the UK trial were seen three times over a six month period at 1, 3, and 6 months. At these visits they were asked how they had felt over the last month, and "no leading questions were asked about specific complaints". This could easily result in an under reporting of BTB. Wiseman, et al. (1984) nevertheless state that the incidence of BTB which they report is higher than that seen in larger treatment trials.

More important than the baseline levels of BTB, however, is the way that bleeding dynamics were effected by prolonged cycles. There was an exponential increase in BTB over the extended cycle in the continuous group, with a substantial rise after the 12th week. One possible explanation for this is poor progesterone receptor function. In order for progesterone receptors in the endometrium to function normally during the menstrual cycle they require priming by unopposed oestrogen. Without this progesterone from the corpus luteum cannot act adequately on the receptors to produce a secretory epithelium. One effect of having *combined* steroid administration from the beginning of the pill cycle is that the proliferative phase lasts only a few days, and the remainder of the cycle is comprised of an extended secretory phase, followed by a few days of relative endometrial atrophy just before withdrawal bleeding (Pincus, 1965).

Baird & Glasier (1991) have argued that unscheduled bleeding on the pill may occur because the endometrium is not exposed to unopposed oestrogen for long enough to give it the capacity to respond to the progestagen. Indeed, the only time during the pill cycle when unopposed oestrogen is present is when endogenous oestrogen is secreted during the pill free interval. Presumably, the consequence of this is that although there is adequate progestagen present, the tissue, unable to "read" it at the receptor level, behaves as if steroid had been withdrawn and bleeds.

In addition to its effects on receptors unopposed oestrogen is also responsible for endometrial repair. It is possible that a poorly repaired endometrium would become increasingly atrophied during extended pill taking. Over the 16 week cycle patches of tissue may have begun to necrose causing more frequent and prolonged bleeding as the cycle progressed. Notably, all three of the Marvelon takers in the continuous group had quite prolonged BTB while those in the other two groups had only a bit of spotting. Perhaps receptor damping occurs more readily in women already accustomed to desogestrel.

BTB did not seem to relate to the amount of endogenous E-3-G that women produced. The association was not considered on a cycle to cycle basis to determine whether or not those women showing marked oestrogen recovery during a pfi avoided BTB during the subsequent cycle. However, substantial endogenous oestrogen has been documented during Marvelon use, which did not correlate consistently with breakthrough bleeding (Kuhl, Gahn, Romberg, März & Taubert, 1985). The cause of BTB during pill cycles remains unclear, but it is apparent that it is impractical to attempt to withhold vaginal bleeding for more than 3 months using a low dose combined pill.

6.6.2 Residual Ovarian Oestrogen

Generally speaking the endogenous oestrogen levels seen in the study volunteers reflected the expected degree of pill induced steroid suppression, and were consistent with the pill regimes. There were a few oddities however, that require explanation. One woman in the control group showed peak levels of E-3-G at unexpected times, out of association with withdrawal bleeding intervals. She reported a strange experience in the middle of the study in which she passed a "blob" of tissue transvaginally. She believed it may have been a miscarriage, but her G.P. did not and all of her monthly ßhCG tests were negative. After this episode she had an irregular bleeding pattern including only scant bleeding in week 16, and a missed withdrawal bleed in week 20. She did, however, have breakthrough bleeding in weeks 18 and 22. Her diary keeping was also erratic. It is possible that she was taking her pills irregularly, which would account for unusual hormonal profiles and bleeding patterns. This is unfortunately impossible to verify.

The continuous group showed oestrogen profiles which one would have expected. Only half of this group collected samples, however, which makes it difficult to conclude that all were well suppressed during extended pill taking. Yet, there was no consistent difference in bleeding or subjective state for those with and without samples. For example, the women with low E-3-G levels in this groups were evenly distributed across the four symptom subgroups described in section 6.5.8.2.

The phase shifted group, on the other hand, included three women with very high E-3-G levels, which exceed those normally seen during ovulatory menstrual cycles. It has been noted that missed pills were probably not responsible. In all of the ten cycles E-3-G began to rise during the pill free interval, but for some reason was not suppressed during the first week of active tablet taking as is usual. Kuhl, et al. (1985) measured endogenous steroids and gonadotrophins over three cycles of Marvelon use in 22 women. They found that LH and FSH levels were not significantly different to control and washout cycles, except on pill day 21. Gonadotrophins had recovered fully by the end of the pfi, and oestradiol remained high in 4 out of 22 women. Oestradiol at mid cycle (pill day 11) was substantially higher in these women than it had been in control cycles.

Perhaps for some women in this sample the steroid dose was inadequate to shut down fully pituitary function, and enough gonadotrophin was released to encourage follicular growth. However, the feedback relationship between the ovary and hypothalamus was distorted preventing an LH surge. Spot pregnanediol estimations indicated that ovulation never occurred. Considering the absolute levels of E-3-G which were achieved it is likely that multiple large follicles developed which luteinized, unruptured, late in the cycle. "Follicular cysts" of >/= 30mm diameter have been observed on ultrasound scans in 8% of triphasic pill cycles, with correspondingly high oestradiol levels (van der Vange, et al., 1985). In spite of their uniformly high oestrone levels these women in the phase shifted group had different amounts of BTB and quite distinct symptom profiles, which suggests that although of interest for contraceptive efficacy, endogenous steroids are not fundamentally responsible for the patterns of mood and physical well being observed over the pill cycle.

6.6.3 The Infradian Rhythm: Evidence and Aetiology

Three hypotheses were under test in this investigation using prospective daily ratings of well being. The first stated that there would be continued evidence of regular oscillations in well being during extended pill taking in the continuous group. This cyclicity would constitute the free running period of an in-built rhythm of emotional well being under constant steroid conditions. A proportion of women did indeed show evidence of such a pattern for both moods and physical changes. The second hypothesis, tested by the phase shifted group, proposed that the steroid cycle acts as the primary *zeitgeber* for this endogenous rhythm, and thus after a phase delay of half a cycle subjective state would re-entrain to the new phase length. Again this seems to be borne out by the data.

The third hypothesis which argued that there would be different aetiologies for moods and physical changes was not supported by the data. Physical symptoms were not allied to steroids as was hypothesized. On the contrary, it was predominantly physical symptoms which showed continued circa-monthly oscillation. None of the physical variables responded in a sufficiently uniform manner across women to be wholly steroid driven. The disproof of this hypothesis lends additional credibility to the notion of endogenicity since one would expect physical changes to be less susceptible than mood to the influence of attribution and expectation. This would seem especially likely for breast tenderness and period type pain, as these do not generally occur at times distant from menstruation and are also not readily confused with other physical sensations, as bloating may be. A proportion of women in the continuous group did show chronic breast tenderness and bloating, but also depression. Period type pain usually occurred with bleeding whether scheduled or not.

There was an overall tendency in this dataset for mood profiles to be more difficult to interpret than physical ones. Cyclical physical changes are commonly seen in both women seeking help for PMS and those not reporting PMS (Metcalf, et al., 1990). Therefore, one would expect physical symptoms to be prominent in a study population which was not selected for PMS experience, and cyclical moods might be expected to be less evident. In keeping with this, the PMS Clinic sample (Chapter Five) does seem to show more robust patterns of mood during manipulated cycles, which share the same dynamics as the physical changes in this controlled study sample. In both samples, however, mood cyclicity shows greater variability in phase and amplitude

than physical states over manipulated cycles. But since mood patterns show large differences from one cycle to the next in conventional pill taking and the menstrual cycle this finding is not surprising. What is surprising is that phenomena like period pain were reported at times in the continuous and phase shifted regimes when bleeds were "due" according to the conventional four weekly pill cycle.

The possibility that women had symptoms at particular times because they expected to cannot be discounted, even for physical sensations. The control group show that there was a tendency for the study to affect women badly. Their diaries reveal that all controls were made more irritable by taking part, in the early part of the study, and their side effects lists include bloating, weight gain, headaches, and loss of sexual interest. A woman already taking Marvelon noted all of these physical changes except headaches. Volunteers were asked what had changed during the six months of the study, but not if they felt the study had caused side effects. So the changes reported may or may not have been attributed by women to the manipulations.

6.6.4 The "Marvelon Effect"

One possible reason for women's reactions, both positive and negative may be the formulation. For example, volunteer A5 reported a substantial improvement in her PMS over the study, but this began during the baseline suggesting that either a placebo or formulation effect was at work. Breast tenderness, nausea, loss of libido, fatigue, depression, and weight gain have all been reported in response to Marvelon (Kuhl, et al., 1985; Wiseman, et al. 1984). But others indicate that the incidence of nausea, headaches, breast tenderness, and depression is lower during Marvelon use (Wiseman, et al., 1984; Massi, Ciardetti, Zucconi, Ottanelli, & Braccini, 1986), and that blood loss and pain are reduced (Nabrink, Birgersson, Colling-Saltin, & Solum, 1980). Different individuals show antithetical responses. The fact that the controls who had switched to Marvelon from another pill became "symptomatic" implies that some of the effect may be due to the formulation.

Some women in the two extended groups might also have been suffering from relative steroid overdose. Chronic breast tenderness, bloating, depression, and loss of sexual interest may be due to extended DSG administration. Desogestrel is a potent progestagen with low affinity for androgen receptors (Wiseman, et al., 1984). Progestagens are thought to contribute directly to these particular symptoms (Bancroft

& Sartorius, 1990) through their effect on steroid sensitive target tissues. Although it is only suggestive, one woman with prolonged depression (A7) did describe it as being like an endogenous depression that was worse in the morning, etc.. As with BTB, the three women in the continuous group already taking Marvelon showed a tendency to have other adverse physical reactions like chronic breast tenderness and bloating, which also suggests some sort of changed response to DSG over time.

Desogestrel raises SHBG and therefore di-hydrotestosterone binding capacity (Cullberg, Knutsson, Lindstedt, Mattsson & Steffenson, 1982). Thus DSG may also have anti-androgenic effects. The relationship between testosterone and sexual interest in women is equivocal. It may be important in some women, and chronic DSG may have contributed to loss of libido in the continuous group through this route. Further, Marvelon's potent progestagenic effect on cervical mucous could contribute to a perception of vaginal dryness, which is also libido inhibiting. Two women who reported significant loss of sexual interest during the study indicated low sexual interest at the initial interview, yet others seemed to undergo a genuine change. The factors responsible for women's sexual interest are complex, and will not be elaborated further here, save to note that there may have been a steroid component operating in this study.

6.6.5 Endogenicity: How and Why?

Discounting potential study effects, Marvelon effects, and steroid overdose effects how much evidence does this controlled investigation provide that an endogenous rhythm of well being linked to the steroid cycle is present in women? An inspection of the longitudinal plots of selected variables for the continuous group show evidence of the regular cyclical oscillation of one or more symptoms in 10 out of 16 women. There was a great deal of inter-individual variation in the expression of symptoms over time, but three patterns predominate. Some women showed regular evenly spaced peaks of symptoms, interspersed with basal values (eg. subgroup 4). Others experienced continued cyclicity superimposed on a raised baseline (eg. subgroup 1), while others experienced cyclicity with both changing phase and amplitude (eg. subgroups 2&3).

The lack of uniformity in women's responses is not particularly surprising since cyclical subjective state is rarely highly consistent over time in even the most tightly entrained circumstance. Furthermore, biological rhythms are known to differ markedly across individuals, and would especially do so if the oscillator were only "partially

entrained", or a weak or "slave" oscillation as was proposed in Chapter Five. The patterns described above would be consistent with a model in which a weak endogenous rhythm of well being existed which was entrained by or coupled to the steroid cycle. In a freerunning condition it would show a tendency to loose amplitude and frequency, or even "miss beats" without the stimulatory/reinforcing effects of cyclical steroids. Equally, being steroid sensitive its parameters might show a tendency to worsen in a chronic steroid environment like the one imposed upon it by this experimental design. Further, if it conforms to a relaxation oscillator model, then steroid withdrawal would be prerequisite for symptom relief, which might help to explain the chronic symptom patterns that some women showed.

The reactions of women in the phase shifted group lend strong support to the idea of an infradian well being oscillator. It was important to include this group because they constitute a *driven* system in which the hypothesized entraining mechanism is systematically altered. For this reason, it is not surprising that there was marked similarity of response across individuals in this group. It was demonstrated that, at least physical variables, showed a sustained rise during the phase shifted cycle, were disturbed in the following cycle, and then restored to their original phase relationship to bleeding/steroid withdrawal in the next. While this could be attributed to the transient effects of chronic pill steroids, the rise in symptoms at the time of the would-be bleed in week 26 is not so readily explained. It would seem that not only has re-entrainment occurred, but that it has done so rapidly, and symptoms have thus "anticipated" the new cycle length.

Progressive circadian dysregulation under the influence of progesterone, like that described by Parry (1990), is not able to account for the persistence of moods and physical symptoms seen during this controlled investigation in which steroids were held constant. The study results seem to point to a longer term rhythm which has a steroid independent time-keeping mechanism. Further research will clearly be required to elucidate the properties of the purported oscillator and its causal mechanism.

6.6.6 Cycle Manipulation as a Treatment Tool

Given the evidence that altering the length of the oral contraceptive pill cycle improves well being in a proportion of women how useful might it be as a therapeutic instrument in the treatment of cycle related change? About 20-25% of women in the Clinic and the

controlled study were significantly improved by the manipulations. None of the Clinic patients experienced an absolute remission of their symptoms, but their severity and duration was reduced. One study participant seemed to be relieved of all negative mood during extended pill taking, while others recorded substantial improvements. It is possible that some of their improvement is attributable to the placebo effect, well known for its potency in PMS treatments. Equally, some changes may be attributable to the pill steroids.

Twenty per cent is a quite small proportion, and about an equal number of women were actually made considerably worse by the regimes. Ideally one would like to be able to detect factors which would accurately predict the quality of a woman's response. And the problem of steroid precipitated effects still remains. The concept of improving PMS by altering cycle length seems to be a useful one, but using OCs to do so would appear to have limitations.

A number of women in both samples made anecdotal reports indicating that "tailoring" the length of the pill cycle to their own underlying menstrual cycle length might be beneficial. Two women in the Clinic (9017 & 8735), and one in the study (A15) found that they were least "symptomatic" over long pill cycles which closely approximated the length of their six to seven week menstrual cycles. There is no medical reason that all women should have a 28 day pill cycle. Women certainly show greater variability in cycle length when not using the pill. Doctors in Soviet Georgia have apparently been successfully tailoring monophasic pill cycle length to women's underlying "sexual cycle" for over twenty years now, with an 80% reduction in the so-called nuisance side effects of the pill (Archil Khomariduze, 1991, personnal communication). Unfortunately all of these findings are currently only published in Russian. The implications of these reports are potentially far reaching. If pill related side effects could be simply reduced, it would increase the pill's acceptability and improve continuation rates.

6.6.7 The Acceptability of Cycle Manipulation to Women

The utility of any system which seeks a therapeutic effect on well being by altering the timing of steroid changes, and thus of vaginal bleeding depends on its acceptability. Fear about potential disruptions to the accustomed pattern of bleeding and well being, and poor reactions to the actual effects of manipulations may both limit acceptability.

Overall the acceptability of the study protocol was good. However, women were being carefully monitored and knew they could seek reassurance or drop out if they had difficulties. Many of them did note that they had faith in the efficacy of the pill, which controlled their anxiety. Acceptability would probably have been even greater, however, if women were undergoing changes in cycle length in a non-blind fashion, because they would feel that they had more control over the experience and could plan ahead.

There was a good deal of pregnancy fear. The first missed bleed was often the first experience of amennorhoea for these largely nulliparous women. After the initial failure to bleed, most volunteers tended to relax and accept the changes quite well. This is of theoretical interest because some studies report that women would be unwilling to accept a contraceptive regime which altered their pattern of bleeding, particularly one which made it less frequent (eg. Snowden & Christian, 1983). This study seems to show that without having had any experience of this kind, responses to this question are invalid. Pill use itself tends to alter blood volume and controls its timing. So while women guess that they will not like changes, experience tends to show that they will accommodate them when they do occur. The very regularity of the pill cycle may make the concept of unconventional cycle lengths even more remote. Having said that the women in this study generally accommodated bleed changes, they were highly self-selected by their willingness to take part in a study of this kind. Recruitment was very difficult, and the large number who refused to take part may show that the majority of women would not even try an altered pill regime once. It would, therefore, be inappropriate to generalize from this study alone.

The implications are nevertheless important as this is perhaps the first time that oral contraceptives have been used in a double-blind way to conceal the timing of vaginal bleeding from women. It is vital for the uptake of new innovations in contraception to understand how acceptable women find a method which alters the expected timing of vaginal bleeding. Three new mechanical-steroid techniques of contraception now exist, the vaginal ring, steroid bearing IUCD's, and Norplant®, all of which are likely to alter the pattern of bleeding. Full use cannot be made of these new methods without a better understanding of how to make their effects on bleeding acceptable to women, and this study does provide empirical evidence for a steroidal contraceptive regime in which the timing of bleeding is unknown, or irregular.

6.6.8 The Drawbacks of the Controlled Study

There are a number of limitations of the data reported in this chapter, apart from those already mentioned above, which make findings suggestive, but in no way conclusive. The biggest problem was that only a small number of women took part, and those who did were highly self-selected. In particular, the control group was too small to provide adequate control data. In addition, although a double-blind design was used the pattern of bleeding soon revealed a woman's group allocation to the investigator. Women entered the study having taken a variety of pill formulations over different lengths of time. Some women were already using Marvelon, while others had to switch to it. Having the Marvelon users provided a useful internal control, but mixed pill histories was nevertheless a source of potential confounding.

Other difficulties arise with methodology and analysis. The daily diary form may not have allowed women to accurately describe their subjective state. Each scale possesses a unique meaning to each woman, and the scales are doubtless used in different ways by individuals. Ratings may be influenced by the length of time that one has been keeping them, and one's subjective state when one is making them. It is also not clear the best way in which to analyse the prospective data which they generate.

Ideally one would like to have a means of weighting constellations of symptoms into a few concept variables, and of systematically and reliably removing noise. How, for example, does one account for the influence of day to day hassles and life events in rating scores? The analytic methods used in this chapter were entirely descriptive, and as such lack the support of statistical proof. Without such mathematical parameters it may be difficult to attest to the validity of observations about the data. It may be said in support of these techniques, however, that they were appropriate in a preliminary and exploratory study of this kind. In light of these factors the findings should certainly be interpreted with caution, and not be generalized until confirmed in a larger sample, perhaps using more sophisticated forms of analysis.

6.7 Chapter Summary

Changing the length of the oral contraceptive pill cycle has proved to be a useful and effective experimental tool for studying the properties of an hypothesized endogenous rhythm of well being. A proportion of women do experience persistent cycles of

mood, and particularly physical well being under constant exogenous steroid conditions. This suggests that an infradian rhythm exists with in-built momentum which will freerun in the right conditions. The phase shifted group gave evidence that the purported oscillator may be primarily entrained by cycling steroid hormones. The *period* of the rhythm seems to be approximately one month in duration. There is considerable inter- and intra-individual variation in both the frequency and amplitude of cycling that women show. This implies that the oscillator is weak, and gains most of its force from its entrainment with a dominant pacemaker like the steroid cycle. Much more research needs to be done before its presence is confirmed, but in the meantime minor alterations in the length of the combined OC cycle may be effective in relieving oppressive cyclical changes or minor pill side effects in a proportion of women.

Chapter 7 General Discussion and Suggestions for Further Research

Cyclical change in women's well being is a phenomenon worth explaining for social, scientific, and therapeutic reasons. The research reported in this thesis has explored the potential for a determinist effect of cycling steroids on the central nervous system, described psychosocial factors and beliefs, and investigated the novel theory of a biological clock mechanism in the aetiology of variations in subjective state.

The investigation of residual ovarian function and subjective state showed that all volunteers had persistent ovarian oestrogen production at a low level, which was independent of the variable doses of progestagen in their pill formulation. Twenty per cent of this sample experienced more than 30% change in physical symptoms around withdrawal bleeds, while only ten per cent had changes in mood of this magnitude. However, 75% of women had mood and physical symptom cyclicity of lesser magnitude. Low level change in subjective state with a preponderance of physical symptoms is to be expected from a non-clinical sample of women.

The main finding of this study was that there may be a relationship between certain physical symptoms, notably breast tenderness and bloating, and the level of endogenous oestrogen. There are a number of possible explanations for this relationship. Endogenous oestrogen may have a direct symptom mediating effect on target tissues such that when oestrogen is high breast pain and bloating are low, and vice versa. The overall degree of oestrogen suppression may determine the severity of the symptom. Alternatively, the level of endogenous oestrogen is only a byproduct of the potency of the exogenous steroids. If so, either the exogenous oestrogen or progestagen, or the two in combination exert an adverse effect on target tissues. The temporal pattern of symptoms may be explained by the cumulative effect of pill steroids over the cycle. Symptoms do not appear until the pill hormones have achieved full ovarian, and possibly hypothalamic and pituitary, suppression, or until exogenous steroids have been in the system for a certain minimum length of time. The concept of direct exogenous steroid effects or relative steroid overdose may help to explain those women in the OC cycle length manipulation study who developed chronic symptoms while taking the pill continuously.

An alternative explanation is that the apparent temporal relationship of steroid levels to physical symptoms is spurious. Perhaps symptoms only relate to the events accompanying vaginal bleeding. Physical symptoms in this sample showed a stronger relationship to the phase in which bleeding occurred than to the phase in which oestrogen peaked. Since in the majority of cases the profile of endogenous oestrogen was highly constrained by the day of the pill cycle, the apparent link between breast tenderness and bloating and oestrone at the group level may have occurred by default. The difficulty with a "menstrual" or uterine factor theory is that the mechanisms which control spontaneous menstruation, and hormone withdrawal bleeding on the pill are likely to be quite different. For example, in the absence of any entraining mechanism, there is no endocrine signal, or change in the internal uterine environment during the pill cycle which signals impending bleeding. Given that physical and mood symptoms may appear during active tablet taking, a purely "menstrual mechanism" seems unlikely.

The possibility remains that some threshold level of change in either endogenous or exogenous steroids must be achieved before the CNS responds, and symptoms are perceived. The women in this study whose levels of endogenous oestrogen passed the arbitrary threshold of 30µg/gr Crt. were more likely to retrospectively report that they had PMS. Perhaps there is a phase or dose response curve in CNS sensitivity to cycling steroids which determines whether or not a woman will become symptomatic. However, three women in the phase shifted group of the cycle manipulation study had levels of oestrogen which would exceed any limit for either the pill or menstrual cycle, and their symptom experience did not differ from women who had extremely low levels of endogenous steroid, throwing this hypothesis into question.

The theoretical basis for the investigation of the effects of pill cycle length manipulation was that, rather than exerting mechanistic drive, the steroid cycle has a facilitatory effect on cyclical well being. The hypothesis that cyclical fluctuations in mood and physical change would persist during constant steroid conditions was supported by the findings. Equally, there was evidence that the steroid cycle acts as an entraining agent in the timing of this infradian oscillation in well being. Mood and physical symptoms did not appear to have different aetiologies. Indeed, physical changes were more robust than mood changes in the controlled sample, in keeping with the notion that physical symptoms are more prominent than moods in non-clinical samples, while as one would expect, mood symptoms showed more marked cyclicity in the PMS Clinic patients.

Overall the findings of the double-blind controlled investigation and the PMS Clinic case studies give strong evidence that there is an infradian rhythm of well being which is entrained to the steroid cycle. The large variation across and within individuals however, suggests that this rhythm is weak. Indeed, four months of freerunning conditions are probably not sufficient to conclude that the rhythm is truly endogenous. A longer period of monitoring might reveal that the rhythmicity damps out to extinction after many cycles. Nevertheless, there was no evidence for reduced amplitude or frequency in the rhythm over the investigation in those women who showed clear evidence of symptom periodicity.

There were a number of difficulties inherent in using oral contraceptives to generate freerunning conditions. Firstly, the rate of breakthrough bleeding was very high, particularly after twelve continuous weeks of pill administration. Irregular bleeding is one of the most common reasons for OC discontinuation, and therefore not a tolerable side effect, particularly if cycle length manipulation is to be used for therapeutic purposes. Secondly, chronic steroids seem to induce chronic symptoms in a proportion of women, notably breast tenderness and distension, bloating, depression, and in a few cases migraine headaches. Thirdly, the experimental demands of a double-blind study in which women did not know when bleeds would occur had a clear negative effect on well being, which was evident in the control group. Women are preconditioned by the negative popular image of the pill to be wary of its adverse effects. Even women who decide to take the pill are likely to approach it with a certain trepidation. Finally, the very regularity of the pill cycle may reduced women's willingness to tolerate hormonal cycles of unusual length. While the continuation rate of women in this study was good and was not strongly influenced by the manipulations themselves, recruitment was very difficult and the volunteers were probably exceptional.

In addition to the practical difficulties with the model, is the important problem that it is impossible to remove the confounding effects of the exogenous pill steroids. There is no way to create a steady endocrine state in a naturalistic way. The alternatives to the OC model are likely to possess similar difficulties. For example, one could monitor well being in women who have been ovariectomized, or pharmacologically castrated using a GnRH agonist while giving replacement steroids in a controlled manner. Freerunning could be assessed in both steroid free and constant steroid conditions. Yet

further theoretical and ethical difficulties arise. It is more likely that such manipulations will emulate transitional or pathological hormonal states in non-representative samples of women, than replicate the dynamic endocrine environment of the normal menstrual cycle. And no matter how "ideal" the hormonal manipulation is, it will never be ethical to subject large numbers of healthy women to prolonged hormonal disruptions which have known adverse effects (eg. loss of bone density, endometrial hypo-/hyperplasia) and may have adverse health consequences which are not yet known. In the absence of viable alternatives, the pill probably offers the safest, easiest, and most acceptable model system, in spite of its limitations. It would be extremely desirable to repeat both of the "experimental" studies in this thesis with much larger samples, over a longer time course, in women with prospectively confirmed, marked mood fluctuation.

In addition to the practical difficulties in carrying out such research, the methodological problems of gathering and analyzing time series data for subjective state remain. Having confirmed that there probably is an infradian oscillator, it would be desirable to model the parameters of the rhythm mathematically. The descriptive evidence would be enhanced by statistical proof.

Different women experience their cycles differently. The nature of a woman's subjective experience is undoubtedly influenced by her personality, her expectations of the cycle, her social conditioning, her immediate environment, and her coping mechanisms. It was not within the scope of this thesis to test any specific hypotheses relating to psychosocial factors. Qualitative, reflexive techniques were used to gather information about demographic variables and women's beliefs in order to take a holistic approach to cycle-related experience. Quality research into the way that beliefs and menstrual experience interact is urgently needed. It is very difficult to assess attitudes in an unbiased way. Studies are required which compare different methods of eliciting information, and which allow for complexity and contradiction in the structure of women's beliefs about this complex area. Perhaps broader information will permit the eventual development of typologies that may be used to predict the way in which women respond to and interpret their cycle-related experience. It would be valuable to compare women with different social and cultural backgrounds, demographic characteristics, stress levels, and reproductive histories more rigourously than was possible in this largely homogeneous Edinburgh sample.

The relationship between subjective state and the steroid cycle is variable, individual, and undoubtedly influenced by multiple causes. Given these facts it is, and will remain a methodologically complex area of research. Describing well being in relation to the menstrual or pill cycle is rather like reporting the weather. It can only ever be described with a degree of accuracy, the influences upon it can be enumerated but the degree of their effect at any given time, in any given place varies and is dynamic, and it is difficult to forecast. The validity of the description depends at all times on the level of analysis. Perhaps steroids are the local ambient temperature, the infradian oscillator is the seasons, and societal attitudes and normative expectations about the cycle are global warming. This research is the "weather" for today. The "forecast" will need to take account of an even greater degree of research complexity.

Abdominal Ultrasound Follow-Up to the Study of Folliculogenesis Reported in Chapter Three

In Chapter Two it was noted that ultrasound scanning (USS) has become an increasingly used and valuable tool in the assessment of ovarian follicular development, both within and outside of pill cycles. Size is normally related directly to the amount of oestrogen a follicle produces, and the dynamics of its growth over time to its functional capacity. The risk of escape ovulation and consequent contraceptive failure was not the primary concern of this thesis. It was, however, considered to be a theoretical interest to compare endocrine and morphological indices of ovarian function. In particular no previous study has examined folliculogenesis in women who were well established on oral contraceptives, nor has the appearance of the ovaries of women taking triphasic versus monophasic pills been systematically compared. The abdominal ultrasound scanning (USS) carried out as part of the study of folliculogenesis reported in Chapter Three aimed to address these deficits.

Training, Scanning Protocol and Equipment

It was originally intended that all 20 study participants would be scanned during their second cycle in the study, however this proved impracticable because the equipment was not routinely available at the time. Almost a full year passed before the scanning was carried out. A large proportion of the volunteers were lost to follow-up because they had stopped taking the pill, or for a variety of other reasons discussed in the results section below. Before the study participants were assessed, I carried out a total of 21 practice scans to learn the technique with the aid of 8 local volunteers attending the Royal Infirmary of Edinburgh. Dr. E.L. Yong provide instruction and supervision.

Each study volunteer who was able to participate was monitored over one complete pill cycle. The first scan was carried out within the first three days of the pfi. This was intended to act as a baseline at which the ovaries were likely to be their most quiescent. Scans were made as frequently as practically possible in order to establish the probable pattern of follicular growth, development and regression. The intervals between scans were determined by the observed growth rate of the follicles, and the amount of endogenous oestradiol and gonadotropin present. Most follicular activity was expected to occur during the pfi., and the first week of pill taking. But it was also desirable to account for what Elstein & Killick (1985) call "autonomous follicular development" in the face of declining steroids and gonadotophins late in the cycle. Queenen, et. al. (1980), for example, document the sudden development of a 10 mm follicle on day fourteen of pill taking which "disappeared during the next twenty-four hours". Each woman underwent between 3 and 6 scans during the pfi, and 7 and 10 during active tablet taking, with a total range of between 11 and 16.

Scans were conducted with a real-time sector scanning machine (Diasonics DSI-RF BMS Scotland Ltd.). The machine had both trans-abdominal, and trans-vaginal probes. The vaginal probe gives high resolution to follicles as small as 1-2 mm, thus its use would be desirable in a study where one expects to see predominantly small follicles. However, because vaginal scanning is a physically and psychologically invasive procedure, probably best carried out by a gynaecologist, I was not prepared to undertake it, and all scans were conducted with the abdominal probe.

Volunteers arrived for scanning with a full bladder, as the procedure works by bouncing ultra-high frequency sound-waves off the barrier between tissues of different densities. Aqueous liquids such as urine and follicular fluid appear on the scan as black

areas, implying low echogenicity. A full bladder in effect creates a "window" through the abdominal tissues to the uterus and ovaries below. Both ovaries were visualized in lateral and transverse planes and the diameter of all follicular structures was measured from top to bottom, and right to left using the electronic on-screen callipers. The scanner was fitted with a camera to take instant freeze-frame pictures of the screen image. Photographs were taken of the baseline state, and at intervals over the cycle. The quality of pictures of small follicles is poor, therefore no photographs are reproduced in the text.

Serum Sampling and Steroid and Gonadotropin Assay Techniques

Because the scanning was not concurrent with the diary keeping and urine sampling, each woman was asked to provide a 10 ml. venous blood sample every day that she attended for a scan. I was trained by the nursing staff of Ward 54 in the Royal Infirmary of Edinburgh to carry out the venepuncture. Samples were centrifuged immediately and plasma was assayed the same day by the staff of the Reproductive Endocrine Laboratories (REL), Edinburgh in their routine assays for Oestradiol (E_2), and Lutienising Hormone (LH). Follicle Stimulating Hormone (FSH) was estimated in all the samples in one 3-day assay carried out by Robin Sellers of the MRC Reproductive Biology Unit, Edinburgh using an assay kit purchased from Serono Laboratories.

Conventionally, serum hormones are related to USS. Because there is much more published information about blood levels, urinary hormone levels were not estimated in this phase of the investigation. The urinary E-3-G profile over the cycle closely parallels E_2 (WHO, 1982), and E-3-G like E_2 has a linear relationship with follicular size (Khatkhatay, et al., 1988). The results for plasma may therefore be compared with the E-3-G profiles derived from urine samples during the main study months.

LH estimations were made using two different assays. The daily rapid-LH assay was producing surprisingly high levels for pill takers, although still low relative to the normal cycle, and it was thought that values were being inflated by interference of non-gonadotrophin particulate matter. Thus at the end of each woman's cycle all of her samples were entered into a 3-day assay. With the exception of one woman whose levels were genuinely raised, LH levels in the 3-day assay were more than 2 times lower than those of the rapid assay. The REL normal ranges were used for LH and Oestradiol, and those supplied with the assay kit were used for FSH.

Results of the Ultrasound Scanning Follow-up and Associated Serum Hormone Measures

Ultrasound scanning of the ovaries was carried out to provide a morphological index of ovarian function. Because there was a long delay after the prospective monitoring, scanning became a follow-up exercise. A number of women were difficult to contact, and many of were no longer available to take part. Table 1 below summarizes reasons for drop-out. Altogether, 4 monophasic and 9 triphasic takers were lost to the investigation. One triphasic taker (T4) was eight months pregnant at the time she was contacted having conceived while taking Trinordiol. She said that she had not missed any pills. She was one of the most reliable study participants, and did not miss a single sample or diary over the original two and a half month investigation. If this were a genuine method failure it is difficult to explain in light of her low level, cyclic E-3-G profile (See Figure below). The tenth triphasic taker (T6) attended for four scans but did not continue because she lived outside Edinburgh and did not tolerate venepuncture well, and her data are not reported here. A fifth monophasic taker (M3) was hospitalized just before her scanning cycle for gastro-enteritis, and was not followed-

up. Ultimately five monophasic takers were scanned over one cycle and no triphasic takers, so unfortunately comparison of the two pill types was not possible.

The results for all the volunteers are summarized in the Table 2 below. Between 2 and 7 small follicles were visible on each ovary at each scan. There were usually about 4 follicles present. Only three of the five women had a follicle with a mean diameter of ≥ 9mm: M4 (both sides), M8 (left), M10 (right). In no instance did a dominant follicle appear to be recruited, although the largest follicle in M10 persisted from the fifth day of the pfi until the ninth day of pills.

The oestradiol profiles were largely consistent with the patterns of urinary oestrogen shown during the earlier phase of the study. For example, M10 had relatively high levels of urinary oestrogen which oscillated around a baseline of about 35 ng/mg Crt., and also had the largest follicle on scan which remained for half of the cycle. The Figure shows the E-3-G profiles of those women not illustrated in Chapter Three (Figures 3.07-3.09). Oestradiol levels during the scanning cycle entered the early follicular phase range in two of the women with large follicles (M4 and M10). The overall impression was that oestrogen was low, yet gonadotrophins were surprisingly high for women on the pill. The same two women with high E_2 had early follicular phase levels of LH (3-day assay). This was transient in M4, but persisted through most of the cycle in M10. All five women had follicular phase levels of FSH for at least part of the cycle: M4 all days, M5 days 27-8, M6 days 27-5, M8 days 27-6, M10 all days.

In summary all women showed multiple, small, slow-growing, low-oestrogen-producing follicles on both ovaries throughout the cycle. Maximum follicular size seemed to relate to gonadotrophin levels and no follicles over 9mm were seen after about day ten of pill taking. The sort of ovarian response a woman shows over her pill cycle seems to be consistent within women across time as ovarian morphology in a scanning cycle was intelligible in terms of prior oestrone profiles.

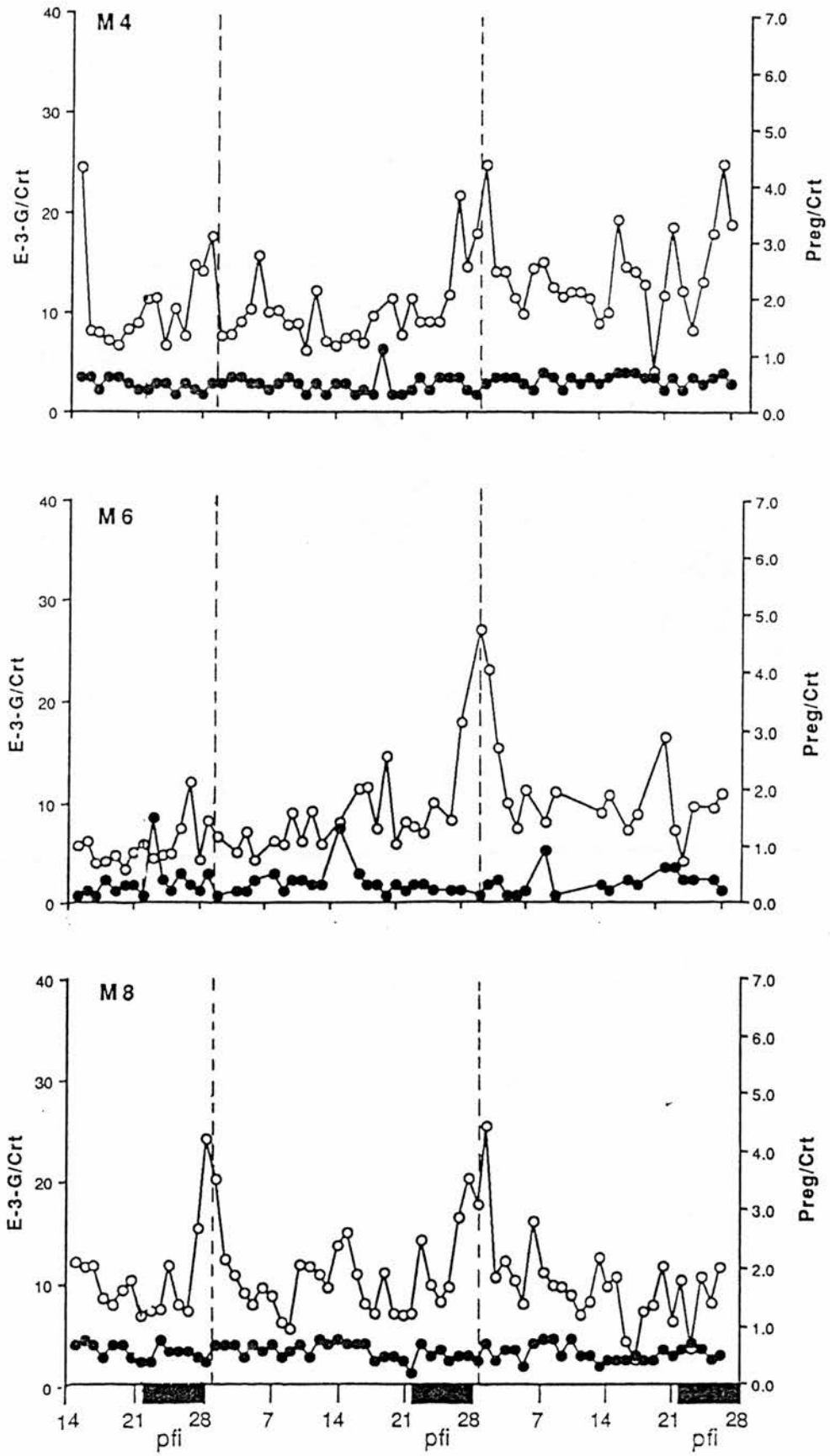
Table 1. Original Volunteers Unable to Take Part in Follow-up

Reason for Drop-Out	Monophasic	Triphasic
Moved out of area	1	1*
Discontinued Pill- Partner sterilized	-	2
Discontinued Pill- Age & Fear of side effects	1*	-
Discontinued Pill- Physical side effects	-	1
Discontinued Pill- Mood / Sexual side effects	1	1
Discontinued Pill- Relationship ended	1	2
Method Failure- Pregnancy	-	1
No time available at present to take part	1	2
Total**	**4**	**9**

* Indicates individuals who's relationships have also ended. **Totals reflect that some women could not take part for more than one reason.

Table 2. Ultrasound and Gonadotrophin Results for Five Monophasic Pill Takers

Volunteer code no.	Pill Day (*bld days)	Oestradiol pmol/l	Rapid LH I.U./l	3 day LH I.U./l	3 day FSH I.U./l	No. Foll's. >2mm left	No. Foll's. >2mm right	Max. Foll. on left	Max. Foll. on right
M4	22 (pfi)	69	4.5	2.03	2.29	no scan	no scan	no scan	no scan
	23 (pfi)	53	5.0	2.24	3.25	3	3	4x4	4x4
	24 (pfi)*	136	4.8	3.03	5.2	4	4	4x6	5x6
	26 (pfi)*	106	7.4	2.87	6.11	4	4	9x10	6x9
	28 (pfi)*	100	8.9	4.14	7.53	5	5	7x7	10X12
	3	42	8.7	3.30	5.42	5	4	7x14	8x8
	5	54	10.2	5.65	7.08	5	5	6x9	7x8
	8	91	9.9	4.71	6.26	5	4	6x11	8x10
	10					3	4	5x9	6x9
	12	42	7.9	3.27	3.26	3	4	6x10	6x7
	15	<30	4.0	1.32	2.13	3	4	8x8	5x6
	17	39		2.68	2.22	3	3	5x7	5x6
M5	24 (pfi)	42	2.2	0.13	<0.50	no scan	no scan	no scan	no scan
	25 (pfi)*	32	2.7	0.13	0.52	-	-	-	-
	27 (pfi)*	64	3.7	0.68	4.07	3	3	4x5	5x6
	3	<30	3.4	1.54	5.18	4	3	7x10	4x8
	4	46	5.0	1.31	5.26	4	3	7x8	5x7
	6	33	0.3	0.19	2.76	4	5	6x7	4x6
	8	33	1.6	0.09	2.07	5	5	6x7	6x10
	11	39	4.0	0.24	0.78	4	5	6x6	3x5
	13	<30	1.4	0.10	0.54	6	2	7x7	6x7
	17	45	4.1	0.24	<0.50	4	3	7x7	5x6
	20	32	2.9	0.12	<0.50	4	2	5x7	4x6
M6	23 (pfi)	<30	3.2	0.13	<0.50	-	-	-	-
	24 (pfi)	37	2.0	0.13	<0.50	2	3	4x4	4x4
	25 (pfi)	43	4.0	0.13	<0.50	-	3	-	5x5
	26 (pfi)	<30	3.1	0.24	0.74	-	3	-	5x5
	27 (pfi)*	<30	4.4	0.36	2.51	3	2	3x3	4x4
	28 (pfi)*	<30	5.5	1.02	6.83	3	-	4x4	-
	1*	71	5.1	1.43	9.6	3	3	7x7	5x6
	2*	55	4.8	0.74	5.5	3	3	8x8	5x7
	3	39	6.4	1.42	4.97	-	-	-	-
	4	<30	4.7	0.65	3.24	3	2	5x7	5x5
	5	34	5.1	1.02	2.68	3	2	4x5	3x4
	7	<30	4.7	1.12	1.52	2	3	5x5	4x5
	10	<30	3.6	0.31	0.76	2	3	5x5	5x6
	14	<30	3.2	0.13	<0.50	2	3	5x5	5x6
	16	37	4.1	0.13	<0.50	-	-	-	-
	21	32	3.3	0.13	<0.50	-	-	-	-
M8	23 (pfi)	<30	4.8	0.18	0.54	3	2	5x5	5x6
	24 (pfi)*	<30	4.2	0.13	0.65	3	-	4x6	-
	27 (pfi)*	81	5.6	2.00	10.75	3	3	4x6	4x5
	2	41	4.3	1.13	4.46	5	3	9x9	8x8
	3	33	4.8	1.36	3.75	3	4	6x9	7x7
	4	41	3.1	0.53	3.18	4	5	8x10	7x9
	5	50	3.1	0.64	2.24	4	3	6x6	6x6
	6	<30	4.4	0.44	2.06	4	4	5x6	5x6
	9	<30	2.9	0.17	0.87	5	5	4x6	5x5
	12	41	1.9	0.92	0.77	5	4	7x9	3x8
	16	57	2.6	0.73	<0.50	5	4	6x7	6x7
	18	45	2.8	0.62	0.51	3	3	7x7	6x8
	20	42	2.9	0.53	<0.50	3	-	4x5	-
M10	23 (pfi)	46	4.5	2.72	2.45	4	3	3x7	5x6
	24 (pfi)*	30	6.0	4.15	3.8	3	4	3x4	5x7
	26 (pfi)*	84	5.1	3.67	4.75	4	4	5x6	9x13
	27 (pfi)*	67	7.1	4.73	5.19	4	4	6x6	7x10
	28 (pfi)*	165	8.8	5.00	5.82	4	4	6x10	9x10
	2	65	10.7	6.79	3.92	4	6	4x9	6x11
	3	99	13.3	10.66	5.58	4	6	7x8	9x15
	5	90	10.6	8.84	4.29	4	5	6x8	5x10
	6	34	5.5	5.39	3.98	4	5	7x8	8x9
	9	67	4.1	3.12	2.88	6	7	5x8	7x12
	10	48	10.3	7.13	3.37	4	6	7x7	6x7
	13	52	5.3	2.33	2.73	3	4	5x3	5x7
	17	41	5.5	3.03	2.23	3	4	4x6	5x8
	20	<30	3.7	1.62	2.16	4	5	4x6	6x6


M 4
M 6
M 8
E-3-G/Crt
Preg/Crt
0
10
20
30
40
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
14
21
28
7
pfi

RECRUITING LEAFLET

OVER 50 MILLION WOMEN A YEAR TAKE "THE PILL"-
ARE YOU ONE OF THEM ?

Dear Clinic Attender:

Do you take the oral contraceptive pill? Have you been taking your pill for six months or more? If so you may be able to help us.

An enormous number of women worldwide take the pill each year. Its benefits as a contraceptive, as well as, its desirable and undesirable side effects are well known. But there is still a great deal to be learned about how the pill works and how women's bodies respond to it. Not all pill types are the same, nor, of course, are all women.

We would like to know more about how women adjust physically and mentally to the pill that they take, and how this adjustment looks after several months of pill use. We feel that this information will broaden our understanding of women and their individual contraceptive needs, and will help us to learn how to better and more effectively use this very important form of contraception.

If you are taking one of the following brands of pill: Microgynon ®, Ovranette ®, Logynon ®,or Trinordiol ®; are between the ages twenty and thirty-five; and have been taking the same pill for at least six months, then you may be able to help us by participating in our study. The advantage to you is that by the end of the research we will be able to tell you how you individually have adjusted to the pill.

If you think that you might be interested in taking part please contact me before you leave the Clinic and I will give you the full details of the investigation. If I am not in the Clinic just now please write your name, address, and telephone number at the botttom of this leaflet and leave it with the receptionist. I will contact you soon.

Thank you very much.

Erin McNeill
MRC reproductive Biology Unit
37 Chalmers Street
Edinburgh EH3 9EW
Tel: 229-2575 ext.62

NAME:_____
ADDRESS:_____
_____
TELEPHONE NUMBER:_____

INFORMATION SHEET

A STUDY OF LONG TERM PILL USE

Thank you for your interest. Here is some more information about why we are doing this study and what you would need to do if you decided to participate.

The study is aimed at women who have been taking the pill for some time. We would like to find out what sort of physical and mental experiences you are having while taking the pill, and how well your pill is suppressing the activity of your ovaries. It may be that while your pill is effectively keeping you from getting pregnant your ovaries are not completely 'shut off'. This means that your body may still be manufacturing its own hormones.

We wish to know if this has any effect on the way that you are feeling. The information that we gather from this study may help us to know which pill is best suited to which woman, which might benefit you as well as others.

We would like to monitor each woman for about two and a half months, over at least two pill cycles. There will be some questionnaires for you to fill in at the beginning, and one or two informal chats spaced over the time of the study. You will need to collect daily urine samples first thing in the morning in small bottles which we will provide. These must be stored in a freezer or the freezing compartment of a fridge for periodic collection. You will also need to fill in a simple 'diary' form each night before you go to bed with scales that measure how you have felt that day . These will be collected at the same time as the urines.

Neither of these last two procedures is time consuming. We hope that you will find them quick and easy to carry out, and that they will not interfere with your daily schedule.

Rest assured that all of the information you give us will be confidential, including your name, address, and telephone number. No questionnaire or 'diary' which you fill in will have your name on it; names and addresses will be kept separate.

Whether you take part or not will not influence the care that you receive at the Family Planning Clinic. If you do finally decide you wish to take part we will ask for your consent to send a brief letter to your general practitioner to let her/him know that you are involved in the study.

If you think you would be interested in taking part, please contact me, and I will give you more details about what the study involves and answer any questions that you might have.

I look forward to hearing from you soon.

Erin McNeill
MRC Reproductive Biology Unit
Centre for Reproductive Biology
37 Chalmers Street
Edinburgh EH3 9EW
Tel: 229-2575 ext.62

MENSTRUAL HEALTH AND REPRODUCTIVE ATTITUDES QUESTIONNAIRE

G1) Please give today's date Day/mo./yr. ___/___/___
G2) Please give your date of birth. ___/___/___
G3) Please give your age. ☐☐

G4) Do you have a paid job?
- Yes, full-time ☐
- Yes, part-time ☐
- No ☐

If yes what is your job? _____
If no, how do you spend your time? _____
_____
Have you had a full-time paid job in the past? What was it?
_____

G5) Are you?
- Single ☐
- Married/Living with partner ☐
- Separated/Divorced ☐
- Widowed ☐

If married/living w/ partner, what is your partner's job?
_____

G6) Whose is the supporting income?
- Yours ☐
- His ☐
- Both ☐

Other _____

G7) Please tick the answer which best fits your case.
- Left school aged 14-17 ☐
- Obtained A-levels, Highers ☐
- Attended College, Polytechnic, or University ☐
- Earned postgraduate or professional degree ☐

G8) Do you practice a religion?
- Yes ☐
- No ☐
- Prefer not to answer ☐

If yes, which one? _____

G9) How frequently do you worship?
- Daily ☐
- Weekly ☐
- Several times a month ☐
- Several times a year ☐
- Rarely or never ☐

G10) Which religion, if any, does your partner practice? _____
G11) Which religion, if any, do your parents practice? _____

C1) Which Pill are you now taking? Name: _____

C2) Would you please describe, as accurately as possible, your history of Pill use. Give dates where possible, or ages when your started taking the Pill and when you stopped. Please indicate the type (e.g.-combined vs. progesterone only) of Pill, and its brand name if you know it. Include all the different times you have taken it, from the first to the present.

_____
_____
_____
_____
_____
_____

C3) Why did you start using the Pill the first time?
C4) Why do you use the Pill now?

(Use column one for C3, and column two for C4. You may tick more than one answer.)

	C3	C4
Contraception	☐	☐
Painful periods	☐	☐
Heavy periods	☐	☐
Irregular periods	☐	☐
PMS (Premenstrual symptoms)	☐	☐

Other reason _____

C5) What time of day do you normally take your Pill?
- Morning ☐
- Before bed ☐
- No special time ☐

Other _____

C6) Do you ever forget to take pills?
- Yes ☐
- No ☐

Do you ever take your pill later than normal?
- Yes ☐
- No ☐

C7) Thinking of your last two packets of pills, have you taken any pills late? (within 12 hrs. of the time you normally take it)?
- Yes ☐
- No ☐

How many

Have you missed any pills in the last two packets? (i.e.- taken more than 12 hrs. late or not at all)
- Yes ☐
- No ☐

How many

C8) Have you looked into the risks and benefits of Pill taking at all yourself, beyond what your doctor has told you?

- Read a book about it ☐
- Talked to other women ☐
- Read an article in a woman's magazine ☐
- Pressed your doctor for more information ☐
- Read other literature, pamphlets, etc. ☐

In some other way_____

_____

C9) Do you ever worry about taking the Pill?

- Yes, I worry a great deal and consider stopping the Pill. ☐
- Sometimes, but there are more benefits to me at this time than risks, so I do not worry overly. ☐
- No, I think the risks are exaggerated and I am not worried that anything will happen to me. ☐

Comment _____

_____

C10) Can you name three advantages of taking the Pill, other than reliable contraception?

1) _____
2) _____
3) _____

B1) What date did your most recent monthly bleed start? ___/___/___

B2) How many days bleeding do you usually have?
(Considering your bleeds in the last six months) Usually ☐☐ days

If the number of days changes from cycle to cycle please note your shortest and longest bleeds in the last six months.

Shortest ☐☐
Longest ☐☐

B3) How many days are usually full flow? ☐☐ days

B4) Do you pass clots when bleeding?

- No, not at all ☐
- Yes, often ☐
- Yes, occasionally ☐
- Not while using the Pill but previously, yes ☐

B5) Overall, how would you describe your blood loss?

- Light ☐
- Moderate ☐
- Heavy ☐
- Very heavy ☐

B6) In the last six months what was the usual number of days from the start of one bleeding period to the start of the next? (i.e.- Cycle length)

☐☐ days

If the number changes from one bleeding episode to another, please note the shortest and longest in the last six months.

Shortest ☐☐
Longest ☐☐

B7) Is the amount that you bleed on the Pill different from when you were not taking it?

- Pill makes bleeding heavier ☐
- Pill has no effect on amount of bleeding ☐
- Pill makes bleeding lighter ☐
- Not sure or cannot remember ☐
- Other _____

B8) If there has been a change, is it acceptable to you?

- Yes, I like it ☐
- No, I do not like it ☐
- No preference ☐

B9) Do you bleed/have spotting/breakthrough bleeding while taking pills?

- Never ☐
- Some cycles ☐
- All cycles ☐
- Have in past, but do not anymore ☐

If yes, how long do you normally bleed/spot? ☐☐ days

B11) What was your reaction? (You may tick more than one) I was:

- excited ☐
- pleased ☐
- proud ☐
- frightened ☐
- upset ☐
- confused ☐
- embarassed ☐
- not bothered ☐
- I do not remember ☐

Other_____

B12) What was your mother's (or female guardian's) reaction? She was:

- excited ☐
- pleased ☐
- helpful ☐
- embarassed ☐
- encouraging ☐
- upset ☐
- angry ☐
- joking ☐
- indifferent ☐
- I did not tell her ☐
- I do not remember ☐

B13) If you did not tell her, do you remember why not?

_____

B14) Did she help you to use protection (pads or tampons)? Yes ☐ No ☐

If not, who did?

- Sister ☐
- Friend ☐
- No one/self ☐

Other _____

B15) Do you think it is important to bleed regularly? Yes ☐ No ☐

Why?_____

_____

What would you feel if you did not bleed?_____

_____

B16) Do you feel that regular bleeding is a part of your being a woman?

- Yes, essential ☐
- No, not necessary ☐
- Not particularly important ☐

Comment _____

_____

B17) Would it be **unfeminine** if you did not bleed? _____

dangerous _____

unnatural _____

B18) Do you resent that you have to bleed monthly?_____

_____

B19) Do you envy the fact that men do not bleed?_____

_____

B20) Would you tell someone if you did not bleed? (e.g.-your partner, a friend, your doctor) _____

B21) If you could eliminate monthly bleeding for a time with no harmful physical consequences, would you do so?

- Very likely ☐
- Possibly ☐
- Not likely ☐
- Definitely not ☐

B22) Have you ever taken more than 1 packet of pills to postpone or eliminate bleeding? Or shortened the number of pill free days between packets? Or otherwise altered you pill cycle?

- Yes ☐
- No ☐

If yes, in what way? _____

_____

B23) Do you feel the same way about the bleeding you experience on the Pill as you did about your menstrual bleeding before the Pill_____

_____

If no, in what ways are they different?_____

_____

B24) If you do not bleed during the pill free week, what does this mean to you?

_____

_____

B25) Over the last 3 cycles how much pain have you had when bleeding?

- None ☐
- Mild to moderate ☐
- Severe pain ☐

B26) Do you use painkillers for this pain? Yes ☐ No ☐

If yes, how often do you use painkillers?

A few cycles ☐
About half the cycles ☐
Many/all cycles ☐

Are painkillers effective in controlling your pain?

Not usually ☐
About half the times used ☐
All/most of the times used ☐

B27) Does the Pill have any effect on this pain?

Has no effect on pain ☐
Was not getting pain at the time of starting Pill ☐
Not sure/cannot remember ☐
Makes bleeding more painful ☐
Makes bleeding less painful ☐

B28) Do you ever have this type of pain when not bleeding and when taking pills?

Always ☐
Some cycles ☐
Never ☐

B29) Does pain while bleeding affect your daily activities ? Yes ☐ No ☐
(i.e.-work, chores, leisure)
If yes:
a) How often does this pain interfere with your activities?
(i.e.-reduce work performance or lower enjoyment of social life, etc.)

Nearly all/all cycles ☐
Fairly often ☐
Occasionally ☐
Never ☐

b) How often is the pain so severe that it prevents you from carrying out your normal activities? (i.e.-have to take time off work or go to bed)

Nearly all/all cycles ☐
Fairly often ☐
Occasionally ☐
Never ☐

c) How do you feel about the way the pain you experience while bleeding affects your activities?_____

_____

B30) On this page is a list of feelings, symptoms and changes which you may or may not have experienced, Before, During, or After your last bleed. If you are having a bleed at the moment or finished one less than five days ago, report on the previous bleed. Please put a NUMBER in each box to indicate whether you have experienced that symptom and if so how severe it was. The number will indicate how severe that symptom is at that time of your cycle.

Any symptom should be scored 0-5
0-no symptom 1-very mild 2-mild 3-moderate
4-severe 5-very severe

Put 0 in the box for no symptom at that time.
Put a number in each box to indicate how you felt around your last bleed.

Example of how to answer:
If you felt moderately nauseated and sick the week before, found the nausea was very severe during, and you were free of it in the week after your bleed, then you would answer as follows:

	Week Before	During Bleed	Week After
Nausea and Sickness.....	3	5	0

	WEEK BEFORE	DURING BLEED	WEEKAFTER
a) Headaches.....	☐	☐	☐
b) Feel bloated in the abdomen.....	☐	☐	☐
c) Feel depressed.....	☐	☐	☐
d) Period type pains.....	☐	☐	☐
e) Get angry for no good reason.....	☐	☐	☐
f) Easily upset.....	☐	☐	☐
g) Craving for particular foods.	☐	☐	☐
h) General aches and pains.....	☐	☐	☐
i) Irritable.....	☐	☐	☐
j) Feel miserable.....	☐	☐	☐
k) Backache.....	☐	☐	☐
l) Clumsiness, e.g. dropping things	☐	☐	☐
m) Feel tense.....	☐	☐	☐
n) Mood up and down.....	☐	☐	☐
o) Feel bad about myself.....	☐	☐	☐
p) Tender breasts.....	☐	☐	☐
q) Hot flushes or sweat.....	☐	☐	☐
r) Nausea and/or sickness.....	☐	☐	☐
s) Spots, e.g. Acne.....	☐	☐	☐
t) Feel tired, lacking in energy...	☐	☐	☐
u)Weepy/tearful.....	☐	☐	☐
v) Other			
_____.....	☐	☐	☐
_____.....	☐	☐	☐

B31) Has the Pill had any effect on these feelings, symptoms, and changes?

Did not have these experiences at the time of starting Pill ☐
Not sure or cannot remember ☐
Improves symptoms ☐
Has no effect on symptoms ☐
Makes symptoms worse ☐
Other:_____

B32) Considering still the month around your last bleed:

a) As far as your general well being is concerned- Was there a time when you felt at your best or at your worst?

	BEST	WORST
Please tick one answer for 'Best' and one for 'Worst'		
Week before bleed	☐	☐
During bleed	☐	☐
Week after bleed	☐	☐
Other time in month	☐	☐
No particular time	☐	☐
Noticed, but do not remember when	☐	☐

b) As far as interest in sex is concerned- Was there a particular time when you felt it was at its highest or its lowest?
(This question can be answered even if you do not currently have a sexual partner, but may be omitted if you prefer)

	HIGHEST	LOWEST
Please tick one answer for 'Highest' and one for 'Lowest'		
Week before bleed	☐	☐
During bleed	☐	☐
Week after bleed	☐	☐
Other time in month	☐	☐
No particular time	☐	☐
Noticed, but do not remember when	☐	☐
Prefer not to answer	☐	

B33) Do you know what PMS (PMT) is? (premenstrual syndrome/premenstrual tension)

Yes ☐
No ☐

If yes, do you believe you suffer from PMS?

Yes ☐
No ☐
Maybe ☐
Not recently, but had PMS in the past ☐

If you do not believe you have PMS, please go to R1. The questions on this page are to be answered only if you think you may or do now suffer from PMS (PMT).

B34) How long do you think you have had PMS? ☐☐ yrs.

B35) How often does your PMS occur?

Every cycle ☐
Most cycles ☐
Less than half the cycles ☐
Rarely ☐

B36) Is your PMS worse some cycles than others?

Mostly the same ☐
Sometimes PMS is worse ☐
Sometimes PMS is much worse ☐

B37) Does PMS interfere with your activities?

Every cycle ☐
Most cycles ☐
Less than half the cycles ☐
A few cycles ☐
No cycles ☐

B38) How severely do you usually suffer from PMS?

Mild PMS ☐
Moderate PMS ☐
Severe PMS ☐
Varies too much to say ☐

B39) During the month around your last period, were the symptoms you experienced:

Better than usual? ☐
As bad as usual? ☐
Worse than usual? ☐

B40) What is the worst type of change that you usually experience? (Your worst premenstrual symptom) _____

_____

This section concerns any pregnancies you have ever had, even if they miscarried or were terminated. If you have never been pregnant please go to R8.

R1) How many pregnancies have you had altogether? (including miscarriages, etc.)
No. of pregnancies ☐☐

R2) What happened in each of your pregnancies? Please tick one answer for each pregnancy. (Think of them numbered in order 1st, 2nd.)

	PREGNANCY					
	1st	2nd	3rd	4th	5th	6th
Live birth	☐	☐	☐	☐	☐	☐
Miscarriage	☐	☐	☐	☐	☐	☐
Abortion	☐	☐	☐	☐	☐	☐
Still birth	☐	☐	☐	☐	☐	☐

R3) When were your pregnancies? Please give the year in which each pregnancy ended, e.g. year of births, abortions, etc..
Year ☐☐1st ☐☐2nd ☐☐3rd ☐☐4th ☐☐5th ☐☐6th

R4) Did you breastfeed after any of your pregnancies?
Yes ☐
No ☐
If yes, after which pregnancies? _____

If you did breastfeed, please also note the baby's age when you first gave it solids or cups, bottles of milk on a regular basis (as near as you can remember).
Baby's age in week : 1st☐☐ 2nd☐☐ 3rd☐☐ 4th☐☐ 5th☐☐ 6th☐☐

R5) Did you enjoy breastfeeding?
Yes ☐
No ☐
Comment:_____
_____

R6) Did you feel depressed for a week or more during the 6 months after the end of any of your pregnancies?

	1st	2nd	3rd	4th	5th	6th
No depression	☐	☐	☐	☐	☐	☐
Depressed for a few days afterwards	☐	☐	☐	☐	☐	☐
Depressed for more than a week but not badly	☐	☐	☐	☐	☐	☐
Very depressed but did not seek medical help	☐	☐	☐	☐	☐	☐
Very depressed, saw doctor about it	☐	☐	☐	☐	☐	☐

R7) If you already have children do you wish to have others?
Yes ☐
No ☐
How many more ☐

R8) If you do not yet have children would you like to in the future?
Yes ☐
No ☐
How many ☐
Don't know ☐

Understanding that this is a difficult question to answer, please respond to the best of your ability:-

R9) In the unlikely event that you became pregnant while taking the Pill, would it be?:
Terrific- I wanted to get pregnant soon anyway. ☐

Good- An unconscious decision would be made for me. ☐

O.K.- A surprise, but something I could adjust to. ☐

Bad- There is no room in my life for a pregnancy at this time ☐

Catastrophic- Impossible, and dangerous to me emotionally and otherwise in my present life circumstances. ☐

Comments-_____
_____
_____
_____

M1) Have you ever been treated by any doctor for Anxiety? Yes ☐ No ☐

If yes, please tick which type of doctor(s).

G.P. ☐
Out-patient clinic doctor ☐
Doctor in hospital ward ☐
Counselor ☐
Other:_____

M2) Have you ever been treated by any doctor for Depression? Yes ☐ No ☐

If yes, please tick which type of doctor(s), and answer the following:

G.P. ☐
Out-patient clinic doctor ☐
Doctor in hospital ward ☐
Counselor ☐
Other:_____

a) Have you been treated in the last year? Yes ☐ No ☐

b) What age were you when you were first treated? ☐☐ yrs.

c) How many times have you spent a night or more in hospital for depression? ☐☐ times

M3) Have you ever been treated with **Anti-Depressant drugs**? Yes ☐ No ☐

If yes, please note the following:

	Anti-depressants for: DEPRESSION	ANXIETY	OTHER
PROBLEM			
i) No. of seperate treatments	☐☐	☐☐	☐☐
ii) Longest treatment (in wks.)	☐☐	☐☐	☐☐

M4) Have you ever been treated with **Tranquillizers**? Yes ☐ No ☐

If yes, please note the following:

	Tranquillizers for: DEPRESSION	ANXIETY	OTHER
PROBLEM			
i) No. of seperate treatments	☐☐	☐☐	☐☐
ii) Longest treatment (in wks.)	☐☐	☐☐	☐☐

M5) Have you ever had any other treatments for any psychiatric problems?

Counselling ☐
ECT (shock therapy) ☐
Lithium ☐

Other (please describe): _____

_____

M6) Have you ever attempted suicide or deliberately harmed yourself? Yes ☐ No ☐

If yes, please give details of the reason and circumstances_____

_____

How long ago was this? _____

How many times has this happened?_____

M7) Have you ever been told by any doctor that you have any of the following?

Fibroids ☐
Endometriosis ☐
Pelvic inflammatory disease (PDI) ☐

Any other gynaecological condition (please describe): _____

_____

M8) Have you ever been told by any doctor that you were in a high risk group of Pill takers due to any of the following?

Smoking ☐
High blood pressure ☐
Thrombosis ☐
Family or personal history of Breast or other cancer ☐

Other (please describe): _____

M9) Have you ever had a 'D and C' (dilation and curettage)? Yes ☐ No ☐

If yes, for what reason?: _____

M10) Are you taking any regular Medication or Drugs? (Other than the Pill) Yes ☐ No ☐

If yes, please name the drug(s) and give the reason for taking it (them).

DRUG	REASON FOR TAKING
_____	_____
_____	_____
_____	_____

M11) Have you had any Major illnesses/diseases, or operations in the last five to ten years, or any accident, emergency, or other problem for which you had to go to hospital, either as an inpatient or as an outpatient.

If so, please give the year and describe:

_____
_____
_____
_____
_____

Daily Diary Instruction Sheet

What the Diary is for:
This 'diary' is designed to measure how you have been feeling physically and emotionally over the day. It also contains relevant questions about the timing and nature of your activities. Because we are trying to generate a picture of how the way you feel changes over time, it is important that you fill the diary in completely and correctly each day. We advise that you fill it in each evening before you go to bed, and mark the scales for the way that you felt over the whole day.

How to fill in the Scales:
The scales are designed to measure individual variation over time. Each line is 10cms. long. A mark at zero (0) means that you did not experience that feeling today, or it was as low as it has ever been. The further along the line you make the mark the more of that feeling you have experienced. A mark at ten (10) indicates that you experienced that mood or feeling as strongly as you can ever remember having experienced it. So:

1) The diary should be filled in about the same time each day, preferably before bed, and refer to the previous 24 hrs..
2) You should mark the scales for how you felt over the whole day including the previous night, (i.e.-all the time since you last filled in a diary), not necessarily how you are feeling right now.
3) You should not look at the previous day's diary for comparison.
4) You should mark each scale with a vertical line through the appropriate point for how strongly you experienced that particular feeling.
5) You should mark each scale every day.
6) Please note that if you did not experience a particular feeling at all put a line through zero (or circle it), but not just near to it or it will be given a score which may be wrong.

For Example:

V) CREATIVE 0_____10
W) CHEERFUL AND HAPPY 0_____10
X) LACKING SELF CONTROL 0_____10
Y) BLEEDING 0_____10
Z) FLG SXL ATR 0_____10

Specific Instructions:
Although most of the scales are self-explanatory, some require a bit more explanation.

The scale CREATIVE, for example, may mean quite different things to different people, and it is up to you to decide what it means to you. One person may say she feels creative when she wants to draw, paint or write a poem, and another when she is able to think of new solutions to problems, perhaps as simple as what to cook for tea. You may feel creative in your job, at home, or in your dealings with other people. With this and all the other scales you must decide what it.means to you.

The BLEEDING line should be used to note the heaviness of vaginal bleeding during the pill free week. It should also be marked if you experience 'breakthrough bleeding' or 'spotting'. Put a mark through zero (0) or leave it blank if you have no bleeding.

Scales 19, 20, and 21 are to do with your sexuality. Abbreviations have been used to protect your privacy. The full wording would be:

19) FEELING SEXUALLY ATTRACTIVE 0_____...____10
20) SEXUAL INTEREST 0_____...____10
21) SEXUAL ACTIVITY 0_____...____10

YES ☐ NO ☐

	SELF	PARTNER	INTERCOURSE
Please memorize what the abbreviations stand for.	☐	☐	☐

FEELING SEXUALLY ATTRACTIVE refers to how you felt about yourself today, while SEXUAL INTEREST is a measure of how much you thought about or desired sexual contact. SEXUAL ACTIVITY refers to the amount that you enjoyed any sexual contact that you have had in the last twenty-four hours (24hrs.). These three scales should be filled in in exactly the same way as all the others, with a vertical line indicating how strongly you felt.

You should tick the YES box if you have had sexual activity and the NO box if you have not. Please tick the 'S' box if you masturbated, and the 'P' box if you had sexual contact with your partner. You may tick both. Tick the 'I' box if your sexual activity included intercourse.

We hope that you do not feel apprehensive about filling in the information requested here. We are asking for it because it is necessary to the research project; your level of sexual activity may affect your ovarian function.

At the end of the list of scales there are two which have been left blank. These are for any emotions or physical changes which you experience regularly, but which are not covered by the previous scales. Some examples are headaches, spots, or feeling weepy or tearful. (They need not necessarily be negative!) If there is something which you would like to put in, write it in every day and mark it like the other scales, marking at zero when you do not experience it.

Please note whether or not you have taken your Pill each day, even if 'no' means you have forgotten it. Be honest, no one will pass judgement. Missed pills (accidentally, or intentionally during the pill free week) will also have an important affect on your ovarian function.

Note any other drugs taken, physical changes, or important events.

The final question asks you if the way you felt changed over the day. Your answer may help us to make sense of your diary. For example, you may mark energetic and fatigued at the same point on their lines because you were quite energetic in the morning but rather tired in the afternoon.

Finally, if you forget to do your diary, do not go back the next day and fill it in. Score a line through the entire page, and carry on with the following day as normal.

If you have any difficulties or questions please contact:

Erin McNeill
MRC Reproductive Biology Unit
37 Chalmers Street
Edinburgh EH3 9EW
Tel: 031-229-2575 ext.62

SCHEDULE: OPEN INTERVIEW

INTRODUCTION AND BACKGROUND

What I would like to do is talk about some of your thoughts and feelings about birth control and reproduction, and where possible examine how your arrived at your ideas- what factors you feel have been important in influencing you.

So please take your time in answering if you need to, and stop me if you do not understand what I am driving at. I apologize if I repeat some of the questions from the questionnaire, but we have a chance now to talk about them more freely.

CONTRACEPTION AND HORMONAL CONTROL

O.K., perhaps the the easiest place to begin is with the Pill.

THE PILL

How did you choose to take the Pill in the first place?
How have you found taking it?
Do you think there is a particular sort of person who takes the Pill?
Does that describe you?
Some people think taking the Pill is "interfering with nature". What do you think?

HORMONAL CONTROL

Do you think that your hormones affect you? In what way?
Are their affects always the same or do they change over time?
Do you think that there is a "natural" or "right" hormonal state to be in?
What is it?
Some people feel that they control their bodies- others that their bodies control them.
What would you say you feel about yours? Does that feeling change over time?
Would you say you liked your body?

CONTRACEPTION IN GENERAL

What do you think a woman's rights are when it comes to being able to control getting pregnant and having babies?
Where do you think your ideas about this come from.
Do you think that your partner's [husband's] attitude is the same as yours?
How is it different? If yes- Why is that?
Is he like other men in his attitudes? If no- Why is he different?
Do you think he has feelings about the pill in particular? Do other men you know?

PARITY AND GRAVITY

Are your feelings about birth control and your body different now that you have had children [been pregnant]?

MENSTRUATION

Let's move on now to some questions about menstruation. In the questionnaire I asked you about your first period, and the way your family reacted to it- could you just tell me about that again.

ATTITUDE, EXPERIENCE, AND BEHAVIOUR

Is menstruation something you feel able to speak openly about? Who do you talk to about it? Other women? Your partner? Other men? Why or why not?
Do you think menstruation is still a taboo subject? Why?
Do you mind if people know you are bleeding? Why? Who?
If no- So why doesn't a woman who's at work or in the pub just walk to the toilet with a tampax in her hand.
So, what's the difference between having a cold and having a period? People tend to show off a cold and talk a lot about it, but women hide the fact that they have their period when **all of us** bleed regularly?
What do you think is positive about menstruation?
Do you think you are perhaps more aware of your surroundings, or more sensitive before or during your period?
Is there anything that you avoid doing while you are bleeding?
Do you have sex? If not- Why not? Who decides that? You, your partner, both of you?
Do you feel differently about yourself on the days that you are not bleeding from the days when you are not? What about at other times in the month? (Pre- post-menstrually)
Do other people notice the differences?
Do you think about menstruation when you are not bleeding?
What name do you use for menstruation?
Do you use pads or tampons?
Would you change your cycle if you could? (Either the pattern of bleeding or your physical and emotional experiences of it.) Why or why not? In what way?

GENDER IDENTITY

All of these questions have to do with the specific reproductive potential of women. I am interested in how you feel about yourself as a woman.

Do you like being a woman?
Do you think that the people around you expect certain things of you because you are female? What do they expect? Who expects it?
Do you change the way you behave meet these expectations? Do you want to?
Do you think that women are expected to be constant in their mood and behaviour? Are we? Is that a good or a bad thing?
Are men constant? Are they expected to be? Should they be?

PERSONAL EXPERIENCE

RELATIONSHIPS

What sort of relationship do you have with you partner/ husband?
Can you describe it to me? (What are the most important features of it?)
Do you feel you have particular roles that you follow?
Does that have anything to do with the sort of person you are?

OPTIONAL: SEXUALITY

When did you start having sexual relationships?
How would you characterize yourself sexually?
How would you characterize your present sexual relationship?

WRAP UP

Is there anything I have not asked you about which you think is important, and will help me to understand you better- Some specific experience or event in your life perhaps that has influenced your attitudes?
One final question- What do you think really motivated you to take part in this study?

(Thanks, and remember to mention the ultrasound.)

REPRODUCTIVE ATTITUDE AND EXPERIENCE QUESTIONNAIRE

This questionnaire aims to find out how women feel about their own experience of contraception and having periods. There are a number of general questions at the beginning about age, work, education, etc., followed by more specific questions about your current contraceptive method, how you chose it, and your experience of your cycle and your periods. We are particularly interested in your attitudes to contraception and menstrual bleeding. We would like to hear the views of women of all ages, using all types of contraception.

There are two parts to the questionnaire. part one takes about 15 minutes, and part two about 5 . Please fill them out while you are waiting to see the doctor. Do not let the questionnaire delay you going up to see the doctor, but if you do not finish before you are called upstairs you may wish to take it with you, as you may have a few minutes to wait there as well.

It is important that you answer all the questions. Please put a tick or a number in the boxes, or give a written response as appropriate. Place your finished questionnaire in the box at reception.

Please try to finish part one before you leave the Clinic. If you do not finish either part one or part two we would be grateful if you could take a "Freepost" (no postage needed) envelope from reception and post us the completed questionnaires.

You are under no obligation to complete this questionnaire, but we would be very grateful if you would do so, as it will be of considerable help to our research. If you do not understand a question please ask for help at reception.

Thank you for your help.

Erin McNeill

MRC Reproductive Biology Unit
37 Chalmers Street
Edinburgh
EH3 9EW

Tel: 031-229-2575 ext. 62

QUESTIONNAIRE NO:

GENERAL QUESTIONS

1) Please give today's date. Day/ Mo/ Yr ____/____/____

2) Please give your date of birth. Day/ Mo/ Yr ____/____/____

3) Do you have a paid job?

- ☐ Yes, full-time
- ☐ Yes, part-time
- ☐ No paid job
- ☐ Full-time student

Could you please specify what job it is you do, or how you spend most of your time:

_____

4) Please tick all of the following which apply to you, (e.g.- Married & Living w/ partner).

- ☐ In a relationship
- ☐ Not in relationship
- ☐ Married
- ☐ Separated/ divorced
- ☐ Widowed

- ☐ Living w/ partner
- ☐ Not living w/ partner

5) What is your partner's job? _____

6) Please tick the answer which best fits your case (Your highest educational achievement).

- ☐ Left school aged 14-17
- ☐ Obtained A-levels / Highers
- ☐ Attended College
- ☐ Attended Polytechnic
- ☐ Attended University
- ☐ Earned a postgraduate degree
- ☐ Earned a professional degree

7) Do you consider yourself to be a religious person? ☐ Yes ☐ No

Are you currently active in your religion? ☐ Yes ☐ No

What is your religion? _____

8) Is your partner religious? ☐ Yes ☐ No

Is he currently active in his religion? ☐ Yes ☐ No

What is his religion? _____

CONTRACEPTION

9) Which method of contraception are you using at the moment?
And which methods have you used in the past?

	Present	Past
Oral Contraceptive/ the Pill	☐	☐
IUD or Coil	☐	☐
Diaphragm or Cap	☐	☐
Condom or Sheath	☐	☐
Spermicide alone	☐	☐
Withdrawal	☐	☐
Rhythm method	☐	☐
Vaginal ring	☐	☐
Other: _____	☐	☐

If you are not using one of these methods right now, is that because?:

You have been sterilized	☐
Your partner has been sterilized	☐
You have had the menopause	☐
You are not in a sexual relationship	☐
You wish to become pregnant	☐
Other reason- Please specify: _____	

10) Altogether, how long have you used your present method of contraception? ☐☐ Yrs/Mos

11) This question concerns the method of contraception that you are using just now. Please tick one answer for each statement made below. Indicate whether:
1) this is something which you like about your method
2) is something you don't really like about it,
3) it does not affect your desire to continue using it,
4) or it does not apply in your case.

If you are not using a method at the moment, or are sterilized please reply to the statements which apply to you, or tick the last box in the row for 'does not apply in my case'.

	Encourages me to use it	Puts me off it	Doesn't affect me either way	Does not apply in my case
• It is easy to use	☐	☐	☐	☐
• It is not messy	☐	☐	☐	☐
• It is separate from intercourse	☐	☐	☐	☐
• It is in my control	☐	☐	☐	☐
• I feel sure it will prevent pregnancy	☐	☐	☐	☐
• It will protect me from sexually transmitted diseases	☐	☐	☐	☐
• It does not affect my hormones or my system	☐	☐	☐	☐
• It involves both my partner and me	☐	☐	☐	☐
• My doctor advises me to use it	☐	☐	☐	☐
• I feel it makes my periods lighter, less painful, or more regular	☐	☐	☐	☐
• I feel it makes my PMS better	☐	☐	☐	☐
• It means I do not have to insert something into my vagina	☐	☐	☐	☐
• It means I do not have an object inside me	☐	☐	☐	☐
• It is associated with intercourse so we have to think about it before we have sex	☐	☐	☐	☐
• It is cheap	☐	☐	☐	☐
• It does not require a doctor's prescription	☐	☐	☐	☐
• It is free from side effects	☐	☐	☐	☐
• It suits my life style	☐	☐	☐	☐
• It is a permanent solution	☐	☐	☐	☐
• My partner likes it	☐	☐	☐	☐
• Most of my friends use it	☐	☐	☐	☐
• I have had problems using other methods	☐	☐	☐	☐
• For one reason or another it is the only method I can use	☐	☐	☐	☐

Any other comments: _____

_____

12) If you do use the Pill now: Which pill do you take? _____

How long have you taken this Pill? ☐ Yrs. ☐ Mos.

13) If the Pill is not your current method, have you used it in the past?

Never used it
Used it for a total of ☐ Yrs. ☐ Mos.

14) What age were you when you started to take the Pill the very first time? ☐☐ Yrs old

PREGNANCY

15) How many pregnancies have you had? (Including miscarriages, etc) ☐☐

16) What happened in each of your pregnancies? Please tick one answer for each pregnancy, and indicate the year of the pregnancy.

	Live Birth	Miscarriage	Abortion	Still Birth	THE YEAR
1st Pregnancy	☐	☐	☐	☐	☐☐
2nd Pregnancy	☐	☐	☐	☐	☐☐
3rd Pregnancy	☐	☐	☐	☐	☐☐
4th Pregnancy	☐	☐	☐	☐	☐☐

MENSTRUAL BLEEDING

17) What age were you when you had your first period? ☐☐ Yrs. old

18) Did you feel prepared for your first period?

- ☐ Well prepared
- ☐ Somewhat prepared
- ☐ Poorly prepared
- ☐ Totally unprepared

19) Who helped you to use protection (Pads, tampons, etc.)

- ☐ Mother
- ☐ Father
- ☐ Sister
- ☐ No one / Self
- ☐ Friend
- ☐ Friend's parent
- ☐ Teacher
- ☐ Other relation (please specify): _____

20) What sort of protection do you use now when you bleed?

- ☐ Pads
- ☐ Pads with tampons
- ☐ Pads or tampons
- ☐ Nothing
- ☐ No need for protection
- ☐ Tampons with applicator
- ☐ Tampons w/out applicator
- ☐ Sponges
- ☐ Other: _____

21) Overall, how would you describe the amount you bleed?

- ☐ Light
- ☐ Moderate
- ☐ Heavy
- ☐ Very Heavy

22) How long is your cycle normally? (i.e.-The number of days from the start of one bleeding period to the start of the next. e.g.- 27 days, 36 days)

Shortest ☐☐ Days
Longest ☐☐ Days

23) What is the **total number of days bleeding** you usually have? Usually ☐☐ Days

24) If the **number of days changes** from one cycle to another, please note the shortest and longest bleeds in the last six months.

Shortest ☐☐ Days
Longest ☐☐ Days

25) How many days are usually **full flow**? Usually ☐☐ Days

26) Would you say that you have predictable cycles?

- ☐ They are always the same number of days
- ☐ They vary by 2-3 days
- ☐ They vary by 5-6 days
- ☐ They vary by more than 10 days

27) Do you have spotting or breakthrough bleeding?

- ☐ Never
- ☐ Some cycles
- ☐ All cycles
- ☐ Have in the past, but not anymore

28) Do you feel it is important for a woman to have periods? ☐ Yes ☐ No

29) Different women give different reasons for believing that it is or is not important to have periods. Please indicate the extent to which each statement below reflects your own beliefs about the importance of having periods.

	Strongly Agree	Agree	Not a Belief I hold	Disagree	Strongly Disagree	Does not Apply in my case
• It is natural	☐	☐	☐	☐	☐	☐
• It is a sign of good health	☐	☐	☐	☐	☐	☐
• It reassures me that I am fertile	☐	☐	☐	☐	☐	☐
• It reassures me that I am not pregnant	☐	☐	☐	☐	☐	☐
• It reassures me that I am using my contraception properly	☐	☐	☐	☐	☐	☐
• It is a nuisance	☐	☐	☐	☐	☐	☐
• It is unnecessary when using reliable contraception	☐	☐	☐	☐	☐	☐
• It is cleansing physically	☐	☐	☐	☐	☐	☐
• It is cleansing emotionally	☐	☐	☐	☐	☐	☐
• It makes me feel a woman	☐	☐	☐	☐	☐	☐
• It is normal	☐	☐	☐	☐	☐	☐
• It is a habit	☐	☐	☐	☐	☐	☐
• It is a waste of bodily energy and nutrients	☐	☐	☐	☐	☐	☐

• Other: _____

30) Do you ever avoid any of the following while bleeding?

- ☐ Sexual intercourse
- ☐ Other physical activities
- ☐ Cooking
- ☐ Going to houses of worship
- ☐ Swimming
- ☐ Being with people in company
- ☐ Taking a bath
- ☐ Nothing

Other: _____

31) Do you notice that any of these things change over the course of your menstrual cycle with a regular pattern?

Happiness	☐	Coordination	☐
Tension	☐	Concentration	☐
Tearfulness	☐	Bloating	☐
Creativity	☐	Feeling attractive	☐
Period type pain	☐	Anger	☐
Headaches	☐	Feeling good about self	☐
Breast tenderness	☐	Energy	☐
Backache	☐	Sexual activity	☐
Hot flushes/ sweats	☐	Sexual interest	☐
Nausea/ sickness	☐	Spots/ acne	☐
Craving for particular foods	☐	Nothing at all	☐
Other:_____		Other:_____	

32) Do you know what PMS (PMT) is? (Premenstrual syndrome/ tension) Yes ☐ No ☐

33) Do you believe you suffer from PMS? Yes ☐ Maybe ☐ No ☐ Not recently, ☐ but have in the past

34) If you could eliminate periods for a time with no harmful physical consequences and there was some other way of making sure that you were not pregnant, would you do so?

Very likely ☐
Possibly ☐
Not likely ☐
Definitely not ☐

For women who are now on the pill, or who have been in the past:

35) Many women change their pill cycle to suit themselves. Have you ever taken more than 21 oral contraceptive pills in a row to postpone or eliminate bleeding? Or shortened the number of pill free days between packets? Or otherwise altered your pill cycle?

Yes ☐ No ☐

How many times ☐
How long ago? ☐ yrs. ☐ mos.
☐ yrs. ☐ mos.
☐ yrs. ☐ mos.

Please explain what you did, why you did it, and what happened each time:

_____

_____

_____

Who's idea was it that you alter your cycle?

My own ☐
A friend's ☐
My partner's ☐
My doctor's ☐
Other: _____

IF YOU ARE ON THE PILL AT THE MOMENT-
WE WOULD LIKE YOUR HELP

Usually women who are on the pill take their oral contraceptives in a standard way with 21 pills in a row and then a seven day break. The people who invented the pill designed it this way because they guessed that women would consider this fairly 'normal', but there is no real medical reason why the Pill should only be taken for 21 days at a stretch.

We are conducting a study of how different lengths of pill cycle affect the way women feel. We hope to find out if individuals have a particular cycle length which suits them best. We need your help to find this out.. And in the end it may help you personally by finding a pill cycle which is right for you.

If you would like to have more information about the study, or think you might like to take part, please print your name, address, work and home telephone numbers below and I will contact you. I will treat this information as confidential. I look forward to talking to you soon.

Yours sincerely,

Erin McNeill

NAME:_____
ADDRESS: _____
_____
_____
_____
_____POSTCODE: _____

HOME TEL: _____
WORK TEL: _____

THANK YOU ONCE AGAIN

SUPPLEMENT TO THE REPRODUCTIVE ATTITUDES QUESTIONNAIRE

The list below includes a number of statements that women have made in interviews about their general attitudes to the experience of having periods. Please indicate the extent to which the statement is one you agree or disagree with by placing a tick in the appropriate box. We would like to have **your own opinion** on each statement, regardless of whether or not you believe these may be views which other women hold.

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
• "My period doesn't tend to affect me, after the first couple of days I tend to forget it's happening."	☐	☐	☐	☐	☐
• "I am just glad to get rid of the blood. I feel like it's all the rottenness in me coming with it."	☐	☐	☐	☐	☐
• "I think other people are embarrassed by tampons and pads so I try to hide them."	☐	☐	☐	☐	☐
• "My menstrual bleeding is private and personal."	☐	☐	☐	☐	☐
• "I feel women's menstrual bleeding is unique. It is not just the body's waste products like urine- blood is life matter-what you're made up of."	☐	☐	☐	☐	☐
• "The men I know just want to forget about that week in the month and talk about the other three."	☐	☐	☐	☐	☐
• "My period is not positive, it's not negative, it's just there."	☐	☐	☐	☐	☐
• "For me menstrual bleeding is just another toilet habit like peeing."	☐	☐	☐	☐	☐
• "I think schools should teach more openly about periods to girls."	☐	☐	☐	☐	☐
• "I quite enjoy bleeding... it gives me a certain relaxed feeling."	☐	☐	☐	☐	☐
• "I believe most people are embarrassed to talk about periods."	☐	☐	☐	☐	☐
• "When I have a painful period it makes me think of bleeding as 'the curse'."	☐	☐	☐	☐	☐
• "I think some of the men I know use the fact that women bleed as proof of their inferiority."	☐	☐	☐	☐	☐
• "I feel dirty when I'm bleeding."	☐	☐	☐	☐	☐
• "I don't think it's morally right to have sex during my period."	☐	☐	☐	☐	☐

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
• "I prefer not to have sex when I have a period because of the mess blood makes."	☐	☐	☐	☐	☐
• "I find that the shared experience of having periods makes me feel closer to other women."	☐	☐	☐	☐	☐
• "I think it is up to parents to tell their daughters about periods, and how to deal with them."	☐	☐	☐	☐	☐
• "My partner is sensitive and understanding when my period affects me badly."	☐	☐	☐	☐	☐
• "I think boys should be taught as openly about periods as girls."	☐	☐	☐	☐	☐
• "I think the act of putting in, and taking out tampons is interpreted by some people as being sexual."	☐	☐	☐	☐	☐
• "I think bleeding brings women an awful lot closer to mortality or to physicalness than men ever need to be. It's a constant reminder that you're flesh and how your body works."	☐	☐	☐	☐	☐
• "I was more embarrassed about menstrual bleeding when I was younger than I am now I'm older."	☐	☐	☐	☐	☐
• "Menstrual blood has a distinct smell which I can detect on myself and other women."	☐	☐	☐	☐	☐
• "I think girls ought to be taught or shown how to use tampons."	☐	☐	☐	☐	☐
• "Basically, I think periods are to do with sex and having babies."	☐	☐	☐	☐	☐
• "I would be embarrassed if I bled onto my clothing."	☐	☐	☐	☐	☐
• "I particularly enjoy sex when I am bleeding, as I am especially sensitive and responsive then both physically and emotionally."	☐	☐	☐	☐	☐
• "I think my partner believes periods must be painful because he associates blood with pain, injury, and trauma."	☐	☐	☐	☐	☐
• "Having a period gives me a feeling of pride in my womanhood."	☐	☐	☐	☐	☐
• "I don't like to have sex when I'm bleeding because I don't like to get blood on my partner."	☐	☐	☐	☐	☐
• "I feel different about my period now I have had children."	☐	☐	☐	☐	☐

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
• "In my experience, some men do not take my views seriously when they think I am having a period."	☐	☐	☐	☐	☐
• "I think women should get tampons and pads on the NHS."	☐	☐	☐	☐	☐
• "I feel the more a woman bleeds the more she is affected by it."	☐	☐	☐	☐	☐
• "I am aware when other women are bleeding without them telling me."	☐	☐	☐	☐	☐
• "Overall, I view my period as a positive experience."	☐	☐	☐	☐	☐

Do you have any comments to make about these statements, or any of your own views about menstrual bleeding that you would like to share?

_____

_____

_____

_____

_____

Please return in the Freepost Envelope provided to:

MRC Reproductive Biology Unit
37 Chalmers Street
Edinburgh EH3 9EW

Results of the Supplemental section of the MHRAQ-2: results given for a random consecutive sample of 500 Family Planning Clinic volunteers

	% Agree	Neutral	Disagree	% missing
The Nature of Bleeding				
• "Basically, I think periods are to do with sex and having babies."	**32**	30	30	8
• "I feel women's menstrual bleeding is unique. It is not just the body's waste products like urine- blood is life matter-what you're made up of."	19	**48**	25	8
• "I think bleeding brings women an awful lot closer to mortality or to physicalness than men ever need to be. It's a constant reminder that you're flesh and how your body works."	25	**39**	28	8
• "My menstrual bleeding is private and personal."	**44**	36	15	6
• "I feel the more a woman bleeds the more she is affected by it."	**49**	29	14	8
Bleeds are Embarassing				
• "I think other people are embarrassed by tampons and pads so I try to hide them."	22	26	**46**	6
• "I believe most people are embarrassed to talk about periods."	**45**	17	31	6
• "I was more embarrassed about menstrual bleeding when I was younger than I am now I'm older."	**77**	8	8	7
• "I would be embarrassed if I bled onto my clothing."	**76**	9	8	7
Bleeds as Neutral				
• "My period doesn't tend to affect me, after the first couple of days I tend to forget it's happening."	**57**	11	27	5
• "My period is not positive, it's not negative, it's just there."	**62**	19	13	6
• "For me menstrual bleeding is just another toilet habit like peeing."	32	24	**38**	6

	% Agree	Neutral	Disagree	% missing
Bleeds as Positive				
• "I quite enjoy bleeding... it gives me a certain relaxed feeling."	6	24	**65**	6
• "Having a period gives me a feeling of pride in my womanhood."	10	**41**	**41**	8
• "Overall, I view my period as a positive experience."	27	**38**	27	7
Bleeds as Negative				
• "I am just glad to get rid of the blood. I feel like it's all the rottenness in me coming with it."	7	28	**60**	6
• "When I have a painful period it makes me think of bleeding as 'the curse'."	31	22	**40**	6
• "I feel dirty when I'm bleeding."	22	17	**55**	6
Bleeding and Sex				
• "I don't think it's morally right to have sex during my period."	11	22	**62**	6
• "I prefer not to have sex when I have a period because of the mess blood makes."	**56**	14	24	7
• "I think the act of putting in, and taking out tampons is interpreted by some people as being sexual."	9	30	**55**	8
• "I don't like to have sex when I'm bleeding because I don't like to get blood on my partner."	18	31	**43**	8
• "I particularly enjoy sex when I am bleeding, as I am especially sensitive and responsive then both physically and emotionally."	12	35	**45**	7
Awareness of other women's bleeds				
• "Menstrual blood has a distinct smell which I can detect on myself and other women."	28	27	**38**	8
• "I am aware when other women are bleeding without them telling me."	10	22	**60**	8
• "I find that the shared experience of having periods makes me feel closer to other women."	19	**44**	29	7

	% Agree	Neutral	Disagree	% missing
Perceptions of men's views				
• "The men I know just want to forget about that week in the month and talk about the other three."	13	19	**61**	6
• "I think some of the men I know use the fact that women bleed as proof of their inferiority."	5	23	**66**	7
• "In my experience, some men do not take my views seriously when they think I am having a period."	18	31	**43**	8
• "I think my partner believes periods must be painful because he associates blood with pain, injury, and trauma."	15	30	**48**	8
• "My partner is sensitive and understanding when my period affects me badly."	**72**	15	6	7
Instruction about periods and equipment				
• "I think schools should teach more openly about periods to girls."	**86**	7	1	6
• "I think it is up to parents to tell their daughters about periods, and how to deal with them."	**76**	11	7	7
• "I think boys should be taught as openly about periods as girls."	**82**	10	3	7
• "I think girls ought to be taught or shown how to use tampons."	**66**	23	4	8
• "I think women should get tampons and pads on the NHS."	**63**	13	17	7

Legend:

Numbers in bold represent the majority view. In some case the majority of women responded neutrally which may indicate a number of things: 1) the statement just doesn't apply to most women- eg. a question about children, 2) women have never considered the idea, 3) women are undecided in their opinion, or 4) the statement is too escoteric and is meaningless to most women.

DIARY BOOKLET

DAILY DIARY FOR SEVEN DAYS
MONDAY TO SUNDAY

SUBJECT NUMBER ☐☐☐☐

MONDAY'S DATE ☐☐ / ☐☐ / ☐☐

INSTRUCTIONS

1. Please start your diary-keeping on the day asked. If this does not happen to be a Monday just put a line through the earlier unused days (even if this means you use only the last day in the booklet!).

2. Please enter your subject number and Monday's date on the front cover.

3. Each night please rate how you have felt that day for all the items listed. If you happen to forget please complete the diary as soon as possible the next day, or, if you can no longer remember, put a line through that day.

4. Please keep you completed diaries in a safe place until it is time for your to return them.

THANK YOU.

* ——————————————— *

MONDAY

MOOD	Not at all			Moderate		Extremely
Feeling tense	0	1	2	3	4	5
Mood up and down	0	1	2	3	4	5
Irritable	0	1	2	3	4	5
Cheerful, happy	0	1	2	3	4	5
Angry without good reason	0	1	2	3	4	5
Miserable, depressed	0	1	2	3	4	5
PHYSICAL						
Menstrual bleeding	0	1	2	3	4	5
Feeling bloated	0	1	2	3	4	5
Energetic, active	0	1	2	3	4	5
Tender breasts	0	1	2	3	4	5
Period-type pain	0	1	2	3	4	5
Fatigued, tired	0	1	2	3	4	5
.....	0	1	2	3	4	5
.....	0	1	2	3	4	5

DRUGS/MEDICATION

Please note any taken today: .....

NOTES

If anything has happened today which has markedly affected the way you feel ie. sad, happy, worried or angry, please note it in the space on the page opposite.

Case Reports of Premenstrual Syndrome Clinic Patients Receiving Oral Contraceptive Pill Cycle Length Manipulation as Treatment for Premenstrual Syndrome

The following are case summaries for eleven women who attended the Premenstrual Syndrome (PMS) Clinic at the Royal Infirmary of Edinburgh between May, 1988 and May, 1991. Each woman underwent some manipulation of the length of her OC cycle in an effort to moderate adverse cycle-related changes in mood or physical well being. The case summaries are descriptive, retrospective reports derived from Clinic case notes. A description of the individual's clinical experience is usually followed by a consideration of the possible aetiological mechanisms responsible for her reactions to the cycle manipulations. Further theoretical consideration can be found in Chapter Five.

Case No. 8735:

Mrs. H. began attending the PMS Clinic in June of 1987, at age 30. She noted that her worst cyclical symptoms were tearfulness and loss of control, as well as, nausea, vomiting, and pain. She was taking Ovran 30 before she first came to the Clinic, for contraception and to help "regularize" and manage her periods, which are about 42 days when not on the pill. Her PMS was generally less severe on the pill, but symptoms had shifted to the bleeding phase.

Dr. Bancroft decided to ask her to take three packets of pills in a row in an effort to reduce the frequency of her adverse symptoms. For the first three months she was relatively symptom free, but in the second extended cycle she developed mood symptoms and a sensation of bloating after about six weeks of active pills. These symptoms continued to "build-up" or worsen over the remaining three pill weeks. After this Dr. Bancroft reduced her cycle to six weeks of active pills followed by a week off. She found this satisfactory, though she reported a decline in mood ("a blip") at the end of the first packet which gradually improved into the second packet. Her mood began to decline again towards the end of the second packet, worsening until the beginning of the withdrawal bleed, when she experienced relief.

It is interesting to note that the pill cycle length which best suited Mrs. H. was the one which most closely approximated the length of her own non-pill cycle of about six weeks. In this case the improvement may have been achieved by re-entraining her mood rhythm to her underlying menstrual cycle. We do not know if Mrs. H.'s improvement on this regime was sustained, as she was discharged from the Clinic in July 1988 with the intention of stopping the pill to try to conceive.

Case No. 8804

Mrs. B. began attending the PMS Clinic in January 1988, at age 37. She presented at the Clinic with premenstrual irritability and cyclical breast changes. She noted that she had had PMS for about ten years; since the birth of her two children in 1977 and 1979. She was very depressed after the birth of her second child, who is handicapped.

Dr. Bancroft started her on Microgynon as a PMS treatment in March 1988. She noted a big improvement in her breast changes, but was still suffering from irritability which had now shifted away from the premenstrual phase into the pill free interval. Dr. Bancroft suggested trying two packets of pills in a row without a break, in an effort to

eliminate some of the adverse symptom phases.

Mrs. B. reported that while she felt fine during the first three weeks of active pills, she felt ill through the whole of the second three weeks. Her breasts and back were sore, she had period type pain, and felt "uptight" from the fourth to the sixth weeks of pills. After two seven-week cycles, she was returned to a conventional pill cycle. She reported herself that the pill was most helpful with physical symptoms, but had little impact on her emotional cycle.

In this case the most acceptable pill cycle length was also close to Mrs. B.'s non-pill menstrual cycle length of about 27(±2) days, suggesting a similar mechanism was operating as in 8735's case.

Case No. 8843

Ms. G., age 22, came to the Clinic in May 1988 complaining of depression, weepiness, and an inability to cope in the premenstruum. Dr. Bancroft started her on Microgynon as a treatment for her PMS. After one month of pills she returned reporting breast tenderness that lasted throughout pill taking, and weepiness during the pill free interval, prior to bleeding. She had not experienced breast tenderness before starting the pill.

Once again Dr. Bancroft wished to use a protracted pill cycle to eliminate the adverse symptoms which seemed to be clustered in the pill free interval. Ms. G. was planning a two month trip to East Africa over the summer, and therefore it was doubly desirable to reduce the number of bleeds. She was advised to take three packs of pills in a row from June until August and then have a seven day break.

She returned to the Clinic in October, 1988. She had misunderstood our instructions and taken four packs of pills in a row, intending to take a fifth. During the fourth pack she began to have breakthrough bleeding that lasted for about three weeks. She had a pill free interval after this pack, and experienced a heavier than normal bleed. Though she felt somewhat physically drained by the prolonged bleeding, her mood was improved by the regime. She reported that she still had bad times, but felt an overall improvement on the pill in mood, and particularly in her acne. She decided to continue with a conventional pill regime, and felt sufficiently improved to be discharged from the Clinic.

Case No. 8846

Mrs. P. first came to the Clinic in April, 1988. She was thirty-eight years old and had two small children. Her presenting complaint was a life long history of migraine headaches during menstruation. Dr. Bancroft decided to prescribe Microgynon to be taken continuously for nine weeks in an effort to eliminate bleeding, and therefore the associated headaches. Mrs. P. had not taken the pill for about thirteen years. She recalled reacting differently to different formulations, but believed that Microgynon had been an acceptable brand for her in the past.

Since childhood, Mrs. P.'s migraines had begun just prior to bleeding, peaking on the second or third day of menstruation. Over the last year, however, they had been coming at other times as well. Attacks were characterized by frequent vomiting and the need to be bedridden for about 48 hours. She noted that both her mother and maternal grandmother suffered similarly, and that she had experienced a total remission during

both of her pregnancies.

Mrs. P.'s reaction to this regime was quite unfavourable, but the results are very illuminating. She felt fine at the outset, but experienced a migraine and vomiting at the end of the first pill packet, during the time when she would otherwise be having a withdrawal bleed. The migraine ended after about two days, but she felt increasingly unwell during the second three weeks of pills with a noticeable and steady increase in breast discomfort and enlargement. On day nineteen of pack two (cycle day 40) she had a second migraine with vomiting, and was very depressed and tearful which she said was unlike her. She stopped taking the pill at the onset of this attack, and as a consequence had a withdrawal bleed three days later (cycle day 43). On the second day of this bleed she had a severe migraine attack with vomiting which lasted for three full days. She had a fourth migraine twelve days later.

There are a number of possible explanations for Mrs. P.'s response to this regime. It is likely that her migraines' relationship to menstruation is not as a direct result of ovulation, but at least in part, a result of the hormone withdrawal that precedes a natural or pill cycle bleed. This would explain the third migraine she had. Since her migraines have come every thirty days for the last ten years, beginning just before a bleed, expectation might be playing some part in their timing. Alternatively, the regularity of her migraines could be explained by a rigid entrainment of the Migraine cycle to her menstrual cycle. This may be why she had the first and second attacks even though she did not bleed, because the migraine cycle had begun to free run.

Her E-3-G levels during the two months she was on the pill indicate that the pill had taken rapid effect in suppressing ovarian function. Basal levels of endogenous steroids may have been experienced by the body as hormone withdrawal and precipitated the first two migraines by a physiological mechanism. They may also have acted as a modulator which phase advanced the migraine cycle through an oscillator mechanism. The final migraine may have been a result of the general disruption in the timing of the hormonal zeitgeber, which if an infradian oscillator were present as hypothesized, would be the expected outcome of a phase shift of aberrant length which was generated by the seven week pill cycle. It is also possible that these headaches would have come at these times irrespective of any changes that were made to her hormonal cycle, as she had reported that attacks were beginning to come at times other than during menstrual bleeding.

Code No. 8868

Mrs. N. first came to the Clinic in July, 1988 at the age of 32. She had been on the pill since the age of thirteen to moderate painful periods. She came off it in 1986 and conceived her only child within three months. Before the birth of the baby she had experienced breast changes over the cycle, but never any mood changes. Her PMS only really emerged after the birth of her son, and was characterized by depression, irritability, anger, loss of control, and breast tenderness starting on about day seven of pills and worsening until the onset of the withdrawal bleed. Dr. Bancroft considered that the pregnancy had in some way altered her responsiveness to steroidal contraception.

Mrs. N.'s case is complicated by the fact that in about 1983 she experienced the onset of bipolar affective disorder. She had had about five manic episodes which required hospitalization, and had been taking Lithium for about four years. During the time we were seeing her she was also suffering from insomnia, frequent "dizzy turns" (anxiety attacks and ulcerative collitis. The many powerful drugs that she was taking may have

been interacting in some way that we did not fully understand. And her tendency to severe episodes of depression may have clouded the picture of her premenstrual experience, as she also began anti-depressants in January, 1989.

Like other patients attending the Clinic, Mrs. N. prospectively monitored her subjective state by completing a self-rated daily diary, and collected daily urine samples for hormone assay for several months. There seemed to be a close positive relationship between her variations in ovarian oestrogen, and her well being. She showed evidence of considerable liberation from pill suppression as a result of the seven day pill free interval, with peak levels in the preovulatory range achieved by the end of the first pill week. Rises in oestrogen were accompanied by improvement in subjective state, and falls by a steady worsening of her well being.

We considered conflicting hypotheses about the cause of this woman's PMS: 1) that symptoms were a result of oestrogen deficiency; 2) that her symptoms were a consequence of the regular starting and stopping of the pill, a sort of phase delayed on-off mechanism; and 3) perhaps in addition to one of the preceding theories, that she had a mood rhythm rigidly entrained to her hormonal cycle by almost twenty years of strictly timed pill cycles.

Dr. Bancroft decided that lengthening Mrs. N.'s pill cycle might reveal whether or not it was the regularity of cycle length, or fluctuations in steroid hormones which was the most salient factor in her PMS. We decide to take a conservative approach at first and add only one week on at the end of a pack. In addition, Mrs. N. was asked to have just six days off before starting a new pack to try and reduce the degree of ovarian recovery. Mrs. N. reported that while she had premenstrual symptoms during the second and third weeks of pills as usual, she had felt better on the extended regime. However, she was very depressed for about ten days after the end of the bleed, during the time when she would otherwise have been feeling her best.

It was then decided that she should stop the pill. She attended two subsequent appointments over the space of five months in which she showed a marked and sustained improvement in her mood and self-presentation. Her entire manner seemed to have changed from a woman who would barely lift her head at an appointment, to someone who appeared relaxed, confident and happy, but not at all manic. She said that she felt better than she could remember feeling in years, and that others had commented. "They must be able to see it in your eyes", she said. Mrs. N.'s dramatic improvement in affect after stopping the pill may have been due in part to the removal of some interaction between the pill and the Lithium she was taking to treat her affective disorder. Alternatively, she benefited from the restoration of high endogenous steroid levels. She stated that she still experienced some PMS, but that it was much less severe and prolonged, which along with her reaction to the attenuated pill cycle suggested to us the presence of a mood oscillator. Perhaps her cycle-related depression was successfully postponed (phase delayed) by the five week pill regime, but was of exaggerated severity due to the combined effects of a phase-shift and prolonged ovarian suppression. Mrs. N. was discharged from the Clinic in September, 1989.

Case No. 8870

Mrs. B. first attended the Clinic in December, 1989. She had one child and had since been sterilized. Mrs. B.'s was oligomenorrheoic, with periods only once every four to five months. She reported experiencing a two week phase of positive well being after a period, followed by PMS symptoms which increased in severity until the onset of the next bleed several months later. Her symptoms included breast tenderness, irritability,

and a general dislike of others with increasing aggressive feelings, which in the final premenstrual week would culminate in violence towards her husband.

Dr. Bancroft decided to see if the severity of her symptoms could be mitigated by generating more frequent bleeds. She was started on Microgynon in December, 1989 which suppressed her steroid hormones to basal levels. After the first two pill cycles she reported that she experienced one good week after the withdrawal bleed followed by a build up of her usual symptoms during the next two weeks until the onset of the next bleed. While the pill did not prevent symptoms occurring, it did seem to "reset the clock" each month, producing proportionally more good weeks than before. She said she was helped by the knowledge that her symptoms would remit with the onset of bleeding.

At her March, 1989 Clinic appointment Mrs. B. indicated that she was going on holiday for the next fortnight, and did not want to have a PMS episode while away. Because she is sterilized and did not require the pill for contraception, we decided to advance her bleed still further by cutting short the pill cycle. We wished to abolish her PMS symptoms early by using this regime. She stopped active tablets on pill day fifteen and had a seven day break, before resuming a twenty-eight day cycle. She monitored her progress throughout this time with prospective daily self-ratings.

When Mrs. B. returned to the Clinic in June, 1989 she reported that the manipulation had worked as desired, and prevented her symptoms from building up. We suggested that she return to this regime of 15 days-on and 7 days-off, and see if it were possible to eliminate her worst premenstrual week in subsequent pill cycles. I spoke to her on the phone in August, 1989 and she said that she had had a "super month". By November, 1989 she had had four months of twenty-two day cycles, and reported that her PMS was now confined to about two or three days of the cycle. She felt "75% better" and was calmer and "not so short with people".

At her return appointment in July, 1990 Mrs. B. was still feeling well on the twenty-two day pill regime, but her premenstrual agitation and anxiety had returned to the longer duration of about ten days. Nevertheless, she still gained relief as soon as the bleed began. She said she was happier and more settled than she has been. My clinical impression was that her affect had improved, she appeared less strained, more relaxed, smiled more easily, and that her complexion was better. She is still being monitored in the Clinic. It is likely that Dr. Bancroft will change her to a lower dose pill, such as Mercilon, at her next visit because she is thirty-four, smokes fifteen cigarettes a day, and has recently been having palpitations.

Because Mrs. B. did not require the pill for contraception, we were able to investigate the potential benefits of a shortened cycle for her PMS. The manipulation was very much an experimental one at the beginning, since we had no previous experience of its effects. The outcome for this woman was most favourable, and the benefits have been sustained for more than a year. In her case, there is a strong relationship between the onset of bleeding and relief from symptoms. It could be that in this and other cases of cyclical mood change, whatever is responsible for the onset of bleeding, is involved in the control of symptoms. However, the mechanism which initiates menstrual and withdrawal bleeding remains ill understood.

In attempting to explain how the regime might be affecting a centrally controlled mood regulating system to confer its advantage, it is important to consider the fact that though the overall change has been maintained, Mrs. B. has recently reported a bad phase of greater duration, about ten days, compared with a bad phase of about three days when the regime was introduced. This fact suggests that the short cycle improved her mood

state by disrupting the phase relationship between the mood and steroid hormone cycles. The short cycle was continually phase advancing a bleed, and consequently also curtailing the negative mood cycle which had become entrained to her very long natural cycles. The great discrepancy in length between the old and new cycles made it very difficult for the mood cycle to reentrain itself to the pill cycle. Nevertheless, over the course of a year of short cycles, the length of the "symptomatic" phase within the short cycle increased suggesting that a gradual reentrainment took place.

Case No. 8927

This 23 year old woman first attended the Clinic in March, 1989. She began experiencing PMS in the autumn of 1986. Ms. C. was sixteen years old at menarche and started to take the pill when she was 17, so it is unlikely that she ever really had well established menstrual cycles. The pill, which she takes for contraception, is Marvelon.

Her PMS is characterized by mood swings and irritability beginning about ten days before her bleed. Symptoms were worst in the three or four days immediately before a bleed, during the pfi, and gradually improved over the course of bleeding. Prospective diary ratings indicated that her symptoms were of clear premenstrual and menstrual timing. Her "good phase" lasted for about two weeks after the end of a bleed.

Dr. Bancroft decided to extend pill taking by one week in an effort to attenuate the phase of positive well being. Ms. C. reported feeling more irritable, but less depressed on this regime. Her diary data indicated a slight overall improvement in her symptoms. In March, 1989 Ms. C. asked if she could take two additional weeks of pills instead of only one, as she wanted to avoid symptoms while on holiday.

The outcome of this five-week-on-one-week-off cycle was very interesting. During the fifth week of pills, days thirty-one to thirty-five, she was very irritable, and had bad period pain, although she did not bleed. She reported that the pain was more like what she used to experience before she started the pill. Ms. C.'s diary data indicated an overall improvement on the prolonged pill cycle, however, she was not satisfied with the degree of improvement and stopped taking the pill.

It seemed that Ms. C. fared best on a five week pill cycle. Although, she still experienced cyclical mood change during a four-week-on-one-week-off regime, the extra week seemed to extend the number of good rather than bad days. It was also interesting that when her pill cycle was extended by more than a week she experienced her symptoms in the fifth pill taking week, or the would-be bleeding week, and they were more severe than usual. The symptoms remitted at the end of that week.

This pattern suggests that she possessed an endogenous mood rhythm of five weeks duration, linked to the hormonal cycle. When she was on a conventional pill cycle her worst symptoms occurred during week four, bleeding seemed to modulate them, and they disappeared about two days after the bleed finished. Four weeks of pills followed by a withdrawal bleed seemed to be a good marriage of the mood and hormonal rhythms. Perhaps the five-weeks-on cycle was not able to "reset" the timing of the mood rhythm without a withdrawal bleeding week, and thus damp down the severity of the mood changes.

Case No. 8959

Mrs. M. first came to the Clinic in August, 1989. She had been taking Mercilon for about four cycles for her PMS. She has two children and her husband has had a vasectomy. She felt the pill had generally improved her symptoms. When not on the pill, she had cycles of about twenty-two days. She reckoned the pill had lengthened her good phase, and shortened the bad phase to about three days. In October, 1989 her family doctor switched her to Brevinor because she was experiencing a lot of pain in her calves and a loss of sexual interest on Mercilon. Mrs. M.'s case is somewhat clouded by the fact that over the course of time that she was being monitored in the Clinic she was having considerable marital difficulties with a number of separations from her husband.

In January, 1990 Mrs. M. reported that she had tried to take two packs of pills in a row, but that it did not really help, as she still had a "bad patch" when she would have been bleeding. In March, 1990 she expressed doubt about whether the pill was really helping since she was regularly having breakthrough bleeding at which time her symptoms of depression and anger would begin. She told Dr. Bancroft that she had had twenty-two day cycles before the pill, and it was as if her own underlying cycle was "breaking through" in spite of the pill. Dr. Bancroft suggested that she try a short pill cycle of 17-days-on-5-days-off

When she returned two months later she noted an improvement. The symptomatic phase which had been lasting for ten days prior to a bleed on the old regime, was now only a few days long. She reported feeling better able to cope, and noted that going on the pill had seemed to help at first, but that the effect had "worn off" on the conventional pill cycle.

In spite of the improvement generated by a twenty-two day cycle Mrs. M. stopped the pill. After three months off it she reported that she was slightly worse. She is still attending the Clinic, and Dr. Bancroft intends to review her situation in a few months time.

Mrs. M.'s case shares some elements with others. It is notable that she, like others, reported a symptomatic phase during an extended pill regime at the time of the would-be withdrawal bleed. She also seemed to fare best on the pill cycle which most closely approximated the length of her natural menstrual cycle, and stated in her own words that her mood cycle seemed to have a periodicity of its own which was not controlled by the length of the hormonal cycle.

Case No. 8972

Ms. D. first attended the Clinic in October, 1989 at the age of 28. She had been using the pill for contraception on and off for years, and most recently, Marvelon since May, 1989. She noted that her PMS usually begins on about the seventeenth day of pills and lasts until her bleed starts. It is characterized by anger, aggression, irritability, and tearfulness. She has had PMS for five or six years.

Since Ms. D.'s symptoms begin on about day seventeen of pill taking, and remit with bleeding Dr. Bancroft, and I decided to see if a shortened pill cycle was of any benefit. Because she needed the pill for contraception we decided that she should take seventeen active pills, and then have only four days off.

When Ms. D. returned to the Clinic in January she was in her third shortened cycle.

She had noticed an improvement in the first cycle, and had only one day of feeling depressed and tearful in the second cycle. However, she had four days of premenstrual type symptoms, notably anger, after her bleed finished. She commented: "It's as if my body has been tricked for a couple of months and then it woke up and realized that it should be having PMS now." This post-menstrual episode was worse than she had ever known it, and she remarked that she had never had her symptoms after a period before.

Dr. Bancroft advised her to persevere with short cycles for two more months. He anticipated that she would have another "post-menstrual episode", but that it would be less severe as it was not being reinforced. When she returned in April, 1990, Ms. D. reported that she was still getting severe PMS. She noted that the timing of her breast tenderness remained very predictable with respect to the onset of bleeding. Her mood symptoms, however, had adopted a quite unpredictable timing. She was having her usual mood symptoms as severely as ever. but for a shorter time before her bleed. But she was also having a second symptomatic phase after the bleed.

She was returned to a conventional pill cycle. Her symptoms arrived between the seventeenth and nineteenth day of pills and seemed somewhat improved. However, Ms. D. decided to stop taking the pill in July, 1990. After five months off the pill, she reported that her PMS was noticeably worse. Her cycle length ranged from 24 to 27, with a mean of 25 days. She questioned whether "any change (in cyclical hormones) makes it (PMS) different for a while". Though her PMS is worse off the pill, she would like to conceive soon, so will remain off it, and continue to be monitored in the Clinic.

The occurrence of Ms. D.'s symptoms after the onset of bleeding in a truncated pill cycle implies that her endogenous rhythm may have previously been entrained to the conventional pill cycle, and was disrupted by the short cycle. It is difficult to know if the subsequent conventional cycles were better or just the same as the cycles prior to the manipulation. It is also curious that Ms. D.'s PMS was so much more severe after she had stopped the pill, though the length of the cycle is shorter than the pill cycle. Perhaps, her PMS is more powerfully entrained to a short natural or pill cycle, but is unable to link itself so powerfully with the longer 28 day pill cycle which thus modulates the severity of symptoms.

Case No. 8986

Mrs. M. first attended the Clinic in December, 1989 at the age of 30. Mrs. M.'s symptoms include being "nervy", accident prone, bad tempered, tired, lethargic, and having diarrhoea and carbohydrate cravings before a period. She has been on Microgynon for about one year and a half, and says she was "quite suicidal" before the pill. The pill has greatly improved, but not eradicated her PMS, which she considers to be severe. On the pill her symptoms have tended to occur during the pill free interval. Mrs. M. was very depressed after the birth of her only child nine years ago. She lost her interest in sex then, and feels it has never really returned. Relations with her husband are poor.

At her February, 1990 visit Dr. Bancroft suggested she take two packs of pill in a row to try and eliminate the worst symptom phase that occurs during the pfi. Mrs. M. had one seven week cycle, and then interrupted the two pack regime and had two conventional pill cycles. She did this because she predicted that she would be premenstrual before her final nursing exams, and wanted to eliminate this possibility. When she came to the Clinic in August, 1990 she was at day 23 of her seven week pill

cycle, and said she "felt lousy" and was "tempted to have a period to release the tension."

She noted that she had been much improved by the seven week cycle at first, by after the two conventional four week cycles, she was just as symptomatic on the seven week cycle. It is possible that the initial improvement was due to the change in regime, but her mood cycle is now too disrupted with respect to her pill cycle to accommodate the further changes in regime.

Case No. 9017

Mrs. R. first came to the Clinic in May, 1990 reporting that she had had cyclical symptoms since menarche. She had been taking Marvelon since 1987, but had recently stopped for two months due to an operation and found that her PMS was worse. So, she resumed Marvelon in June to control her PMS. Because like many others her worst symptoms occur during the pill free interval, Dr. Bancroft advised her to try a ten week pill cycle. But also in view of the experience of others, he advised that we see her towards the end of the second pill packet, in case she was experiencing a build up of symptoms.

When she came to the Clinic in September, she had had seven and a half consecutive weeks of pills, and was feeling quite well. She noted that both her husband and her mother had commented on the improvement in her mood. She did say that she had had ups and downs, and that "you could probably see where I would have had a period, but it (her diary ratings) was all one's and two's." Overall, her symptoms seemed to be damped down by this regime. Her cycle when not on the pill tends to be fairly long, varying from 31 to 42 days in length. The improvement in her moods was sustained over two subsequent ten-week cycles. While monthly symptoms were diminishing, PMS symptoms had begun to occur in week eight or nine of pills, prior to the withdrawal bleed in week ten. This suggests that she was undergoing a gradual reentrainment to the much longer cycle length.

MRC
Medical Research Council

MRC Reproductive Biology Unit
Centre for Reproductive Biology
37 Chalmers Street
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Telephone 031-229 2575
Fax 031-228 5571

Your reference

Our reference

29th January, 1990

Dear «volunteer»,

Thank you very much for completing our questionnaire at your recent Family Planning visit. I am very grateful that you have expressed an interest in a further study of how women feel when they are using oral contraceptives. We believe that this research may help us to take important steps towards a better understanding of how the menstrual cycle, or in your case the pill cycle, may effect a woman's moods, physical sensations, and reactions to events in her everyday life. I hope that you will be able to help us by taking part in the study.

My name is Erin McNeill, and I am the one who you will speak to and be in contact with during the study if you decide to take part. As you can see from the above address, I am based in the Medical Research Council's Reproductive Biology Unit in Chalmers Street.

Basically what the study involves is having a number of women take one type of combined oral contraceptive pill for a period of six months and report in a systematic way on how they feel over that time. What will be different about the way in which you take your pill is that the pills will be specially packaged so that you just take one everyday without knowing when your "week off" is going to happen. Some cycles may be more than 28 days, but this will have no effect at all on the way your contraception works. I will explain everything that will happen in the study when I first meet with you.

Before we go any further I would like to make sure of a few of your details. First of all it is a lot easier and quicker for me to contact you by phone, especially in the day time. So could you please let me have both your daytime and evening telephone numbers if you have not given them to me already. Could you also tell me exactly how long (as far as you know) you have been on your pill and what its brand name is. And if you happen to live outside Edinburgh, could you let me know how easy it would be if you took part in the study for you to come in for interviews and check-ups about once a month. Please fill out these details on the enclosed bit of paper and return it to me in the freepost envelope. I look forward to hearing from you soon, and to working with you over the coming months.

Yours sincerely,

Erin McNeill

Do you take a Combined Oral Contraceptive Pill ?

Are you between the ages of 20 and 40
(35 if you smoke) ?

Do you notice predictable changes in either
your mood or your physical well-being
or both over your cycle ?

Would you be interested in having
periods less frequently ?

Or

Are you curious to know if a longer pill cycle
might improve some of the physical or mood
changes which you experience over your cycle ?

If the answer to all these questions is Yes, then you may be able to help me:

The people who invented the Pill believed that women consider it normal to bleed every 4 weeks, and for this reason they decided all women should take the pill in a standard way: 3 weeks on & 1 week off. But women who are not on the Pill do not all have cycles of the same length. The length of the cycle can vary a great deal and still be perfectly normal.

The truth is there is no medical reason why the Pill should be taken in this rigid way. Having a Pill cycle longer than 4 weeks will not reduce contraceptive cover or be harmful medically, and it may even have some benefits for your health and well-being.

I am conducting a study on the way that Pill cycles of different lengths affect the way women feel. It may be that individual women need to find a Pill cycle which suits them best individually.

I need your help to answer this question, which may benefit you and other women as well. If you think that you would like to take part in this study, or would like to talk to me about what it involves please leave your name, address, work and home telephone numbers with the staff at reception, and I will contact you.

Or you can phone me on 031-229-2575. Ask for Erin McNeill or leave a message with the switchboard.

I look forward to hearing from you soon.

REPRODUCTIVE ATTITUDE AND EXPERIENCE QUESTIONNAIRE

This questionnaire aims to find out how you feel about taking the Pill and having periods. It should only take you about 10 to 15 minutes to fill in, so you should be able to do it while you are waiting to see the doctor. Do not let the questionnaire delay you going up to see the doctor, but if you do not finish before you are called upstairs you may wish to take it with you, as you may have a few minutes to wait there as well.

It is important that you answer all the questions. Please put a tick or a number in the boxes, or give a written response as appropriate. Place your finished questionnaire in the box at reception.

Please try to finish the questionnaire before you leave the Clinic. If you do not finish it we would be grateful if you could take a "Freepost" (no postage needed) envelope from reception and post us the completed questionnaire.

You are under no obligation to complete this questionnaire, but we would be very grateful if you would do so, as it will be of considerable help to our research. If you do not understand a question please ask for help at reception.

Thank you for your help.

Erin McNeill

MRC Reproductive Biology Unit
37 Chalmers Street
Edinburgh
EH3 9EW

Tel: 031-229-2575 ext. 2490

QUESTIONNAIRE NO:

1) Please give today's date. Day/ Mo/ Yr ____/____/____

2) Please give your date of birth. Day/ Mo/ Yr ____/____/____

3) Please give your Clinic Number ____ ____ - ____ ____ ____ ____

4) Do you have a paid job?
- ☐ Yes, full-time
- ☐ Yes, part-time
- ☐ No paid job
- ☐ Full-time student

5) Could you please specify what job it is you do, or how you spend most of your time:

_____

6) Please tick all of the following which apply to you, (e.g.- Married & Living w/ partner).

- ☐ In a relationship
- ☐ Not in relationship

- ☐ Married
- ☐ Single
- ☐ Separated/ divorced
- ☐ Remarried
- ☐ Widowed

- ☐ Living w/ partner
- ☐ Not living w/ partner

7) What is your partner's job? _____

8) Please tick the answer which reflects your highest educational achievement.

- ☐ Left school aged 14-17
- ☐ Obtained A-levels / Highers
- ☐ Attended College
- ☐ Attended Polytechnic
- ☐ Attended University
- ☐ Earned a postgraduate degree
- ☐ Earned a professional degree

9) Which type of pill do you take?

- ☐ Combined low dose pill (20-35µg Oestr.)
- ☐ Triphasic low dose pill (3 different coluors)
- ☐ Progesterone only pill (Mini pill)
- ☐ Biphasic low dose pill (2 different colours)
- ☐ Combined high dose pill (50 µg Oestr.)

10) Do you know the brand name of your pill? _____

11) How long have you taken this Pill? ☐ Yrs. ☐ Mos.

12) How long have you taken the Pill altogether? ☐☐ Yrs.
(All different brands excluding breaks of 3 months or more.)

13) What age were you when you started to take the Pill? ☐☐ Yrs old

14) What are the main things you like about taking the Pill?

1)_____
2)_____
3)_____
4)_____

15) What are the main things you dislike about taking the Pill?

1)_____
2)_____
3)_____
4)_____

16) How many pregnancies have you had? (Including miscarriages, etc) ☐☐

17) What happened in each of your pregnancies? Please tick one answer for each pregnancy, and indicate the year of the pregnancy.

	Live Birth	Miscarriage	Abortion	Still Birth	THE YEAR
1st Pregnancy	☐	☐	☐	☐	☐☐
2nd Pregnancy	☐	☐	☐	☐	☐☐
3rd Pregnancy	☐	☐	☐	☐	☐☐
4th Pregnancy	☐	☐	☐	☐	☐☐

18) What age were you when you had your first period? ☐☐ Yrs. old

19) Did you feel prepared for your first period?

- ☐ Well prepared
- ☐ Somewhat prepared
- ☐ Poorly prepared
- ☐ Totally unprepared

20) Who helped you to use protection (Pads, tampons, etc.)

- ☐ Mother
- ☐ Father
- ☐ Sister
- ☐ No one / Self
- ☐ Friend
- ☐ Friend's parent
- ☐ Teacher
- ☐ Other relation (please specify): _____

21) What sort of protection do you use now when you bleed?

- ☐ Pads
- ☐ Pads with tampons
- ☐ Pads or tampons
- ☐ Nothing
- ☐ No need for protection
- ☐ Tampons with applicator
- ☐ Tampons w/out applicator
- ☐ Sponges
- Other: _____

22) Overall, how would you describe the amount you bleed?

- ☐ Light
- ☐ Moderate
- ☐ Heavy
- ☐ Very Heavy

23) Do you have spotting or breakthrough bleeding?

- ☐ Never
- ☐ Some cycles
- ☐ All cycles
- ☐ Have in the past, but not anymore

24) Do you feel it is important for a woman to have periods?

- ☐ Yes
- ☐ No

25) Different women give different reasons for believing that it is or is not important to have periods. Please indicate the extent to which each statement below reflects your own beliefs about the importance of having periods.

	Strongly Agree	Agree	Not a Belief I hold	Disagree	Strongly Disagree	Does not Apply in my case
• It is natural	☐	☐	☐	☐	☐	☐
• It is a sign of good health	☐	☐	☐	☐	☐	☐
• It reassures me that I am fertile	☐	☐	☐	☐	☐	☐
• It reassures me that I am not pregnant	☐	☐	☐	☐	☐	☐
• It reassures me that I am using my contraception properly	☐	☐	☐	☐	☐	☐
• It is a nuisance	☐	☐	☐	☐	☐	☐
• It is unnecessary when using reliable contraception	☐	☐	☐	☐	☐	☐
• It is cleansing physically	☐	☐	☐	☐	☐	☐
• It is cleansing emotionally	☐	☐	☐	☐	☐	☐
• It makes me feel a woman	☐	☐	☐	☐	☐	☐
• It is normal	☐	☐	☐	☐	☐	☐
• It is a habit	☐	☐	☐	☐	☐	☐
• It is a waste of bodily energy and nutrients	☐	☐	☐	☐	☐	☐

• Other Comments: _____

26) Do you ever avoid any of the following while bleeding?

- ☐ Sexual intercourse
- ☐ Other physical activities
- ☐ Cooking
- ☐ Going to houses of worship
- ☐ Swimming
- ☐ Being with people in company
- ☐ Taking a bath
- ☐ Nothing

Other: _____

27) Do you notice that any of these things change over the course of your menstrual cycle with a regular pattern?

Happiness	☐	Coordination	☐
Tension	☐	Concentration	☐
Tearfulness	☐	Bloating	☐
Creativity	☐	Feeling attractive	☐
Period type pain	☐	Anger	☐
Headaches	☐	Feeling good about self	☐
Breast tenderness	☐	Energy	☐
Backache	☐	Sexual activity	☐
Hot flushes/ sweats	☐	Sexual interest	☐
Nausea/ sickness	☐	Spots/ acne	☐
Craving for particular foods	☐	Nothing at all	☐
Other:_____		Other:_____	

28) Do you know what PMS (PMT) is? (Premenstrual syndrome/ tension) Yes ☐ No ☐

29) Do you believe you suffer from PMS? Yes ☐ Maybe ☐ No ☐ Not recently, ☐ but have in the past

30) If you could eliminate periods for a time with no harmful physical consequences and there was some other way of making sure that you were not pregnant, would you do so?

Very likely ☐
Possibly ☐
Not likely ☐
Definitely not ☐

31) Many women change their pill cycle to suit themselves. Have you ever taken more than 21 oral contraceptive pills in a row to postpone or eliminate bleeding? Or shortened the number of pill free days between packets? Or otherwise altered your pill cycle?

Yes ☐ No ☐ How many times ☐

How long ago? ☐ yrs. ☐ mos.
☐ yrs. ☐ mos.
☐ yrs. ☐ mos.

Please explain what you did, why you did it, and what happened each time:

1st Time)_____
2nd Time)_____
3rd Time)_____
4th Time)_____

Who's idea was it that you alter your cycle?

My own ☐
A friend's ☐
My partner's ☐
My doctor's ☐
Other: _____

WE NEED YOUR HELP TO FIND OUT MORE ABOUT THE PILL!!

Usually women who are on the pill take their oral contraceptives in a standard way with 21 pills in a row and then a seven day break. The people who invented the pill designed it this way because they guessed that women would consider this fairly 'normal', but there is no real medical reason why the Pill should only be taken for 21 days at a stretch.

We are conducting a study of how different lengths of pill cycle affect the way women feel. We hope to find out if individuals have a particular cycle length which suits them best. We need your help to find this out. And in the end it may help you personally by finding a pill cycle which is right for you.

We would not make your Pill cycle shorter than it currently is, and therefore, the study will not reduce the contraceptive cover the Pill gives to you. It is quite safe, and there is no medical risk.

If you would like to have more information about the study, or think you might like to take part, please print your name, address, work and home telephone numbers below and I will contact you (I will treat this information as confidential). Or you are welcome to tear off the first page of this questionnaire and contact me. I look forward to talking to you soon.

Yours sincerely,

Erin McNeill

NAME:_____
ADDRESS: _____
_____
_____
_____
_____POSTCODE: _____

HOME TEL: _____
WORK TEL: _____

THANK YOU ONCE AGAIN

Encapsulation of "Marvelon" Tablets. For MRC Trial

To produce capsules suitable for a double blind trial Marvelon tablets were packed in opaque gelatin capsules with lactose as filler. Strictly this does not achieve a true "double blind" as the code may be broken by opening of the capsules. Co-operation of investigator and patients to not break the code in this way must be ensured.

The empty capsules were placed in a "labocap" capsule filling machine which holds 100 capsules. These were first approximately half filled with lactose. 100 Marvelon tablets were counted and checked. Using tweezers one tablet was placed in each capsule. The plate of capsules was visually checked by a second person before the capsules were filled with lactose and capped. This procedure was carried out in a cytotoxic cabinet within the non-sterile production area to prevent exposure of the operators to the steroids contained in the tablets.

The capsules were packed in 7s and 2 labels were attached to each bottle - the study label and a peelable content label. The peelable content labels provided a method of reconciliation when coding material.

John R. Young, MRPharmS
Pharmacy Production
St Bartholomew's Hospital
LONDON EC1A 7BE

JY/bt
6/11/90

Daily Diary Booklet

Pill Study No. 2

Lothian Health Board
Protocol No. 89/45

This booklet contains enough diaries to fill one in each day for twenty eight days.

Please complete one form each night just before you go to bed. Try to answer all the questions accurately considering the last 24 hours, or the time since you last filled in a diary.

Please note your study number, and the study weeks covered by this booklet in the space below.

Code Number:

Study Weeks: to

Thank you for your help

Code No: ☐☐☐☐ Date: ☐☐☐ Wk. No.: ☐ Pill No. ☐

	Not at all					Moderate					Extreme	
Bleeding	0	1	2	3	4	5	6	7	8	9	10	☐
Period Type Pain	0	1	2	3	4	5	6	7	8	9	10	☐
Cheerful and Happy	0	1	2	3	4	5	6	7	8	9	10	☐
Irritable	0	1	2	3	4	5	6	7	8	9	10	☐
Aggressive / Angry	0	1	2	3	4	5	6	7	8	9	10	☐
Energetic and Active	0	1	2	3	4	5	6	7	8	9	10	☐
Tense and Anxious	0	1	2	3	4	5	6	7	8	9	10	☐
Feeling Good About Self	0	1	2	3	4	5	6	7	8	9	10	☐
Depressed and Unhappy	0	1	2	3	4	5	6	7	8	9	10	☐
Fatigued and Tired	0	1	2	3	4	5	6	7	8	9	10	☐
Breasts Tender	0	1	2	3	4	5	6	7	8	9	10	☐
Feeling Bloated / Swollen	0	1	2	3	4	5	6	7	8	9	10	☐
Headache	0	1	2	3	4	5	6	7	8	9	10	☐
Craving Particular Foods (e.g. sweet or salty)	0	1	2	3	4	5	6	7	8	9	10	☐
Sxl Intr	0	1	2	3	4	5	6	7	8	9	10	☐
Sxl Actv Y☐ N☐ S☐ P☐ I☐	0	1	2	3	4	5	6	7	8	9	10	☐
_____	0	1	2	3	4	5	6	7	8	9	10	☐
_____	0	1	2	3	4	5	6	7	8	9	10	☐

SIGNIFICANT EVENTS: Did anything happen today to affect the way you feel?

_____

_____

_____

_____

PHYSICAL CHANGES: (Other than those mentioned above)

_____

_____

If you had Bleeding today, do you think it is probably a period or probably just spotting? (Tick one)

A period ☐ Spotting ☐

DRUGS/ MEDICATION: _____

INFORMATION SHEET FOR VOLUNTEERS LHB Protocol 89/45

Welcome to our study of women on the pill.

Why we are doing this study

First let me explain why we are doing this study. The people who invented the oral contraceptive pill decided that women should take it in such a way that they would bleed every 28 days. They decided this because they thought that most women had a cycle that was about 28 days long. The truth is that most women do not have a cycle of exactly 28 days, and for most people the cycle changes in length a good deal from one to the next. Most women will find that they have their own average cycle length, but for one person that may be 35 days while for another it is 26.

The point is not all women who take the pill would be having 28 day cycles if they were not taking it. We wonder if it is right for all women to take the pill in exactly the same way. Maybe some women would feel better physically or emotionally if they took the pill in the way that was most similar to their own average cycle.

How we would be changing your pill taking

You will be involved in the study for about six months (25 weeks of pills). During this time we will give you your pills to take. You will be taking a common, low-dose (30µg oestrogen), combined oral contraceptive pill. This study is what is called "double-blind". This means that neither you nor I will know which study group you have been put in. We will both be 'blind' to the sequence in which you are being given pills to take. A third person, who is helping me to do this research, will know which group you are in. She will have a code to tell her exactly how you are taking your pills.

We cannot tell you what sort of pill cycle you will experience because this might influence the way you report how you feel. But we can say that no one will be taking **fewer** than 21 pills at a time between weeks of dummy pills. So the **minimum** number of contraceptive pills that you would take before having a week off would be 21 just like in the normal pill cycle. The **longest time** that you would take contraceptive pills without a week of dummy pills would be **16 weeks**. There is no medical reason why it is dangerous for a woman to take contraceptive pills for this length of time without a break. The only thing that might happen is that she will have irregular, or breakthrough bleeding.

The pills will be just like your normal contraceptive pill except they will be enclosed in gelatine capsules filled with lactose powder, and packed in small bottles. You will take one pill **every day**. Usually you will be taking a contraceptive pill, but at times when we are giving you a week off you will take a 'dummy pill'. The 'dummy pills' will contain only lactose powder which is the sugar that occurs naturally in milk. Because we do not wish you to know which pills are dummy pills and which ones are active contraceptive pills it will be necessary for you to take one capsule every day. The lactose in the capsules will delay the time it takes for your body to absorb and start using the hormones in the pill by approximately one hour, so you should try to take your pill one hour earlier than you normally do. It is also a good idea to take the pill at the same time each day.

Each bottle will contain one week's supply of pills (7 capsules), and will be labelled with your study code number, and the study week number. It is extremely important that you use the bottles in the **correct order**, that is, you finish all the capsules in the bottle labelled week number one first, before you open week number two's supply. So, you should open bottle **"Wk.1"** first and finish all the capsules in it, then you should open bottle **"Wk.2"** and finish all the capsules in it, and so on like this until you finish **"Wk.25"**, and come to the end of the study. You will be given a five weeks supply of pills each time you come for an appointment (every four weeks) to reduce the chance of bottles getting lost or muddled. You should bring all empty bottles and the open one you are currently using with you when you come up to see me each month.

What else will you have to do

There are a number of things which we would like you to do, as well as taking the specially packed pills, so that we can follow how you are feeling.

1) Meet with me (Erin McNeill) twice for a period of about one hour- once at the beginning and once at the end of the study for an informal interview.

2) Record how you have felt each day on a 'diary form'. (Explained below)

3) Collect a sample of urine first thing in the morning, three times a week. (Explained below)

4) Come up to the Royal Infirmary once every four weeks to give a urine sample for a pregnancy test (just as a safeguard!), and to get more diaries and pills.

Interviews

At the first interview I will explain what the study involves and fill in any gaps in the information about periods and contraception that were not covered by the questionnaire. I will also ask you to fill in a few other short questionniares. In the interview at the end we will talk about your experience in the study. Both meetings should only take about one hour.

Daily Diaries: What they are and how to fill them in

You will be given a booklet each month that contains 28 diary forms, or a 4 week supply. One diary form is to be filled in each night just before you go to bed throughout the study. The answers you give should relate to the way you have felt over the **last 24 hrs.**, since you last filled in a diary. It is important that you do not go back and look at your answers from previous days, and you should fold the booklet in such a way that you can only see the diary form that you are currently filling in. If you forget to do a diary do not try to fill it in the next day; please just put a line through the page you have missed.

The scales cover a number of different emotions and physical states. You should circle or put an 'X ' through one number between zero and ten for each scale. Zero is the least and ten is the most that you have experienced that feeling. Please write your code number, the date, and the number of the pill that you have taken that day in the spaces provided. There are 2 spaces at the end of the scales in which you may include other things which you regularly experience, but which are not on the list. If you do add something you should rate this emotion/sensation every day just like the rest of the scales, even if it is often zero. Please answer the questions at the bottom of the page as well.

There are two scales to do with sexual feelings. The first SXL INTR stands for sexual interest. You should use this scale to record how interested in sex you were today. The other scale SXL ACTV has to do with sexual activity. Please tick Y or N for yes or no if you have had sexual activity today or not. Tick the boxes **S** if you masturbated, **P** if you had sexual activity with your partner, and **I** if this involved intercourse. Circle a number on the scale for how satisfying you found the sexual activity. If you are filling in your diary before you go to bed as you are meant to then you should rate the scales for sexual feelings, and activity that has taken place in the **previous 24 hrs.**, including the previous night (since you last filled in a diary). Obviously if you have not had any sexual activity then please leave this scale blank.

Arrangements can be made for you to return completed diary booklets by Freepost, or our van driver can collect them, though you may find it easiest to just bring the finished booklet with you when you come for your monthly visit.

Urine Samples

We would like you to collect urine samples so that we can measure the reproductive hormones that your own body is producing. We will give you a supply of small bottles to collect your

sample in. Three times each week you should fill one bottle first thing in the morning. Try to collect samples at equal intervals over the week. (E.g.-monday, wednesday, and friday, or tuesday, thursday, and saturday). Mark it in **pencil** (ink will run!) with your code number, the date, and the pill number for that day, and place it in the freezing compartment of your fridge, or deep freeze.

You should bring your frozen samples, completed diary booklets, and used pill bottles with you when you come up to the hospital every four weeks. If you miss an appointment, or cannot make it other arrangements can be made to ensure that we get your sample for pregnancy testing, and that you have a constant supply of pills and diaries.

Additional urine samples for monthly Pregnancy Test

Every four weeks we would like you to come up to the Royal Infirmary to give an early morning urine sample for that day. This should be collected even if you would not normally collect a thrice weekly one that day. We need this sample in order to do a pregnancy test on it. If you are taking your pills one each day as you should there is no risk that you will get pregnant. The main reason we are doing this is **to reassure you**. As we have said, the changes in the length of you cycle may mean that you do not bleed as often as every four weeks. So if we can let you know that you are not pregnant then you should not worry about the fact that you have not had a bleed for a while. We will reimburse you your travel expenses to and from the hospital at the end of the study.

Arrangements for Collection of Diaries and Samples

It would work out quite well if you could bring each month's diaries and urine samples with you when you come for your monthly repeat visits. We can have a chat about how you are getting on and I will be able to give you another month's supply of pills, diaries and sample bottles. If this is not feasible other arrangements can be made.

Medical Adviser

Although we do not expect you to have any problems we have built in a safeguard to deal with any physical concerns that arise. There will always be a doctor available to help you if you have a problem that you feel is related to the study. (Please see names below). This doctor will know which pill cycle you are on, so she will know what to do if you miss a pill or are concerned about your pattern of bleeding.

You **must** contact me or one of these doctors **straight away** if you miss more than one pill so that we can advise you of what to do. If you miss just one pill take it as soon as you remember, or together with the next day's pill.

Please do not hesitate to contact me at any time if you have questions or concerns. I look forward to working with you over the coming months.

Yours sincerely,

Erin McNeill

People to contact in case of a problem:

Ms. Erin McNeill
Centre for Reproductive Biology
37 Chalmers Street
Edinburgh, EH3 9EW
031-229-2575 ext.2490

Dr. John Bancroft
Centre for Reproductive Biology
031-229-2575 ext.2216

Lothian Health Board Protocol 89/45

CONSENT FORM

I have read the information sheet provided, and spoken to the investigator (Erin McNeill). I understand what is required of me, and I agree to take part in this study of the oral contraceptive pill. It has been explained to me that I will not be taking my oral contraceptive as I normally do, but that the changes made for the study will not effect the contraceptive protection the pill gives me.

I know that I may withdraw from this study at any time, for any reason, and that I may refuse to answer any question if I wish.

I agree that my G.P. be informed that I am taking part, and that Erin McNeill may look at my Family Planning Clinic notes if necessary to gain further information.

SIGNATURE: _____

DATE: _____

Letter to General Practitioner

Dear Dr.

Your patient, _____, attended the Dean Terrace Family Planning Clinic recently, and agreed to take part in an ongoing study into the possible benefits of different oral contraceptive cycle lengths for mood and well being which is being conducted through the MRC Reproductive Biology Unit.

The time course of involvment in the study for each individual is a period of about seven months during which time her pill cycle will be altered in a controlled fashion for about four months. This is a double-blind investigation, using placebo tablets during would be pill-free-intervals. Individuals will be allocated to one of three groups: 1) a 'control group' which will have 21 active pills followed by 7 placebos throughout, 2) an 'extended group' who will have one six week pill cycle during the study, and 3) a 'continuous group' who will have a period of 16 weeks active pill administration during the study. These manipulations of the cycle will have no effect on contraceptive efficacy.

We have provided Ms. _____ with a six months supply of Marvelon which Organon International have kindly supplied. The presentation of the tablets has had to be altered in order to achieve blindness. Tablets have been placed in gelatine capsules packed in lactose powder. The lactose does not interfere with pill absorption, but may delay steroid uptake by the gut wall by up to one hour, and women have therefore been advised to take their pill one hour earlier than normal. During withdawal bleed intervals women will be taking a capsule that contains lactose powder alone.

The women have been advised to contact us first in cases of missed pills. Drs. Glasier, West, and Bancroft will be able to break the randomization code if necessary in order to advise a woman of the degree of risk created by an error in pill taking and how to rectify it. The probability that an individual will be late in taking, or miss one or more pills is very high over a six month study period. Therefore we ask your cooperation in contacting us if your patient should attend your surgery for such a reason and it is evident that we have not yet been contacted.

We will conduct a pregnancy test on urine every four weeks. This is not because we forsee any change in the pregnancy risk from that in normal pill taking, but primarily to provide the reassurance of nonpregnancy *in lieu* of a bleeding episode to those women who are on an extended pill regime (see 2 and 3 above). We felt you should know this to prevent causing you unnecessary alarm if a patient were to mention it without explaining the justification.

If you have any queries do not hesitate to contact one of us at the above address. Erin McNeill will be conducting the study and blind to the group to which a woman has been allocated. She will be supervised by Dr. Bancroft. Drs. Glasier, and West will be informed and available at all times to advise on medical issues. We thank you for your cooperation.

Your sincerely,

Erin McNeill
Study Coordinator

Dr. Anna Glasier
Director Well Woman Services, Lothian

Dr. John Bancroft
Consultant Psychiatrist

Dr. Christine West
Consultant Gynaecologist

PILL CYCLE MANIPULATION STUDY:
INTERVIEW SCHEDULE

Initial 1 Hour Interview
Created 14th June, 1990
Erin T. McNeill

1) Sign consent form.

2) Obtain G.P.'s address.

3) Offer information sheet to read and take away.

4) Administer: a) EPI
b) M.H.L.C.S.
c) BDI

5) Pose the following questions,and code responses, adding written comments where additional relevant information is offered.

01) Age 00 ☐☐

02) Smoking habits Yes 1 No 0 ☐ No. per day ☐☐

03) Parity ☐ 1-7 8+
Gravidy ☐

04) Date of last cycle manipulation ☐☐ mo. yr.

05) Length of time on this O.C. ☐☐.☐

06) Length of time since last break from the pill of 3 mos. or more. ☐☐.☐

07) Total length of time on all different pill types ☐☐.☐

08) Number of pills tried ☐

09) Reasons for changing pills in the past:

01 wt. gain / increased appetite	13 weepiness / crying
02 weight loss	14 unusual fatigue
03 acne	15 chronic thrush
04 loss of libido	16 age
05 depression	17 health risks (family history)
06 irregular bleeding	18 pill scare
07 no bleeding / amenorrhea	19 mental disturbance / psychosis
08 worse PMS	20 concern of partner
09 heavier / more painful periods	21 doctor's advice
10 bloating / abdominal pain	22 to give your body a rest
11 headaches	23 to have a child
12 raised blood pressure	24 other

10) Do you feel you have PMS, or predictable changes over the cycle? Yes 1 No 0 ☐

11) Can you please describe to me what normally happens to you over your cycle, both physically and emotionally? *Probe- enumerate list.* Yes 1 No 0

Physical		PrM	M	PsM	IM	Mood		PrM	M	PsM	IM
Ovulation pain	11					Euphoria	20				
Menstrual pain	12					Ingenuity / Creativity	21				
Bloating	13					Insightfulness	22				
Backache	14					Depression	23				
Headaches	15					Irritability	24				
Breast tenderness	16					Low self esteem	25				
Food craving	17					Tearfulness	26				
Body temp. up / flushes	18					Tension / Anxiety	27				
Body temp. down / chills	19					Jealous / suspicious	28				
Urinary frequency / urgency	10					Emotionally strong	29				
Nausea / sickness	11					Pessimistic	30				
General aches & pains	12					Efficient / effective	31				
Spots / acne	13					Sexual interest	32				
Vaginal dryness	14					Easily angered	33				
Clumsiness	15					Emotionally vulnerable	34				
Bursts of energy	16					Other:	35				
Fatigue	17										
Thrush	18										
Other:	19										

12) What are your worst / most pronounced cyclical changes? ☐☐☐☐

13) Has your cycle always been like this? ☐

14) How was it different before you started taking the pill? Use coding above.

Physical		Mood	
More	Less	More	Less

15) How long was your cycle before starting to take the pill? Menarche-20 yrs. 20-40 yrs. ☐☐
(After Treloar, 1967)

16) If parous: Did you breastfeed any of your babies? Yes 1 No 0 [ ]
No. of times [ ]
No. of weeks [ ]

17) Where you depressed during any pregnancy? [ ] Yes 1 No 0

18) Where you depressed after any pregnancy? For how long [ ] wks.

19) Have you experienced any of the following in the past year? Yes 1 No 0

a) Change in employment or working conditions? Self [ ] Partner [ ]

b) Financial difficulties? [ ]

c) Health problems? Self [ ] Close relative / friend [ ]

d) Relationship changes or difficulties? [ ]
1 One partner
2 Several partners
3 Stable / untroubled
4 Unstable / troubled

e) Housing changes or difficulties? [ ]

f) Legal difficulties? Self [ ] Family [ ]

g) Other significant events?

h) Did you get support or help with these difficulties from anyone? [ ]
Partner [ ]
Relative [ ]
Friend [ ]
Professional [ ]

20) Do you consider yourself to be under stress at the moment? [ ]
1 Not at all
2 A little bit
3 Considerable
4 Intolerable

21) Do you feel you are managing your stresses? [ ]

22) Have you ever been treated by a doctor for: [/]

Anxiety	1
Depression	2
Psychosis	3
Other mental illness	4

23) Do you feel you have experienced a severe episode of any of these, but have not sought help or treatment for it? *Coding as above* *No 0* [/]

24) Have you ever deliberately tried to harm yourself? [ ]

25) Have you ever required treatment for any gynaecological condition? No 0 [/] [/]

Fibroids	1	Endometriosis	2
PID	3	Abnormal smear	4
Menorrhagia	5	Cervical erosion	6
STD	7	Other	8

26) Do you have any medical condition not already mentioned? [ ]
Does it require drugs / medication? [ ]

6) Any additional comments:

Arrange next meeting for 5th week of pills.

E ○ N ○ L ○ ☐☐☐☐☐☐☐☐☐☐

FORM B

		YES	NO
1.	Do you like plenty of excitement and bustle around you?	○	○
2.	Have you often got a restless feeling that you want something but do not know what?	○	○
3.	Do you nearly always have a "ready answer" when people talk to you?	○	○
4.	Do you sometimes feel happy, sometimes sad, without any real reason?	○	○
5.	Do you usually stay in the background at parties and "get-togethers"?	○	○
6.	As a child, did you always do as you were told immediately and without grumbling?	○	○
7.	Do you sometimes sulk?	○	○
8.	When you are drawn into a quarrel, do you prefer to "have it out" to being silent, hoping things will blow over?	○	○
9.	Are you moody?	○	○
10.	Do you like mixing with people?	○	○
11.	Have you often lost sleep over your worries?	○	○
12.	Do you sometimes get cross?	○	○
13.	Would you call yourself happy-go-lucky?	○	○
14.	Do you often make up your mind too late?	○	○
15.	Do you like working alone?	○	○
16.	Have you often felt listless and tired for no good reason?	○	○
17.	Are you rather lively?	○	○
18.	Do you sometimes laugh at a dirty joke?	○	○
19.	Do you often feel "fed-up"?	○	○
20.	Do you feel uncomfortable in anything but everyday clothes?	○	○
21.	Does your mind often wander when you are trying to attend closely to something?	○	○
22.	Can you put your thoughts into words quickly?	○	○
23.	Are you often "lost in thought"?	○	○
24.	Are you completely free from prejudices of any kind?	○	○
25.	Do you like practical jokes?	○	○
26.	Do you often think of your past?	○	○
27.	Do you very much like good food?	○	○
28.	When you get annoyed, do you need someone friendly to talk to about it?	○	○
29.	Do you mind selling things or asking people for money for some good cause?	○	○
30.	Do you sometimes boast a little?	○	○
31.	Are you touchy about some things?	○	○
32.	Would you rather be at home on your own than go to a boring party?	○	○
33.	Do you sometimes get so restless that you cannot sit long in a chair?	○	○
34.	Do you like planning things carefully, well ahead of time?	○	○
35.	Do you have dizzy turns?	○	○
36.	Do you *always* answer a personal letter as soon as you can after you have read it?	○	○
37.	Can you usually do things better by figuring them out alone than by talking to others about it?	○	○
38.	Do you ever get short of breath without having done heavy work?	○	○
39.	Are you an easy-going person, not generally bothered about having everything "just-so"?	○	○
40.	Do you suffer from "nerves"?	○	○
41.	Would you rather plan things than do things?	○	○
42.	Do you sometimes put off until tomorrow what you ought to do today?	○	○
43.	Do you get nervous in places like lifts, trains or tunnels?	○	○
44.	When you make new friends, is it usually *you* who makes the first move, or does the inviting?	○	○
45.	Do you get very bad headaches?	○	○
46.	Do you generally feel that things will sort themselves out and come right in the end somehow?	○	○
47.	Do you find it hard to fall asleep at bedtime?	○	○
48.	Have you sometimes told lies in your life?	○	○
49.	Do you sometimes say the first thing that comes into your head?	○	○
50.	Do you worry too long after an embarrassing experience?	○	○
51.	Do you usually keep "yourself to yourself" except with very close friends?	○	○
52.	Do you often get into a jam because you do things without thinking?	○	○
53.	Do you like cracking jokes and telling funny stories to your friends?	○	○
54.	Would you rather win than lose a game?	○	○
55.	Do you often feel self-conscious when you are with superiors?	○	○
56.	When the odds are against you, do you still usually think it worth taking a chance?	○	○
57.	Do you often get "butterflies in your tummy" before an important	○	○

BECK INVENTORY

Name: ..... Date: .....

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad or unhappy that I can't stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I don't feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. 0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

8. 0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9. 0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10. 0 I don't cry anymore than usual.
    1 I cry more now than I used to.
    2 I cry all the time now.
    3 I used to be able to cry, but now I can't cry even though I want to.

11. 0 I am no more irritated now than I ever am.
    1 I get annoyed or irritated more easily than I used to.
    2 I feel irritated all the time now.
    3 I don't get irritated at all by the things that used to irritate me.

12. 0 I have not lost interest in other people.
    1 I am less interested in other people than I used to be.
    2 I have lost most of my interest in other people.
    3 I have lost all of my interest in other people.

13. 0 I make decisions about as well as I ever could.
    1 I put off making decisions more than I used to.
    2 I have greater difficulty in making decisions than before.
    3 I can't make decisions at all anymore.

14. 0 I don't feel I look any worse than I used to.
    1 I am worried that I am looking old or unattractive.
    2 I feel that there are permanent changes in my appearance that make me look unattractive.
    3 I believe that I look ugly.

15. 0 I can work about as well as before.
    1 It takes an extra effort to get started at doing something.
    2 I have to push myself very hard to do anything.
    3 I can't do any work at all.

16. 0 I can sleep as well as usual.
    1 I don't sleep as well as I used to.
    2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
    3 I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0 I don't get more tired than usual.
    1 I get tired more easily than I used to.
    2 I get tired from doing almost anything.
    3 I am too tired to do anything.

18. 0 My appetite is no worse than usual.
    1 My appetite is not as good as it used to be.
    2 My appetite is much worse now.
    3 I have no appetite at all anymore.

19. 0 I haven't lost much weight, if any lately.
    1 I have lost more than 5 pounds.
    2 I have lost more than 10 pounds.
    3 I have lost more than 15 pounds.

    I am purposely trying to lose weight by eating less.
    Yes _____ No _____

20. 0 I am no more worried about my health than usual.
    1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
    2 I am very worried about physical problems and it's hard to think of much else.
    3 I am so worried about my physical problems, that I cannot think about anything else.

21. 0 I have not noticed any recent change in my interest in sex.
    1 I am less interested in sex than I used to be.
    2 I am much less interested in sex now.
    3 I have lost interest in sex completely.

MULTIDIMENSIONAL HEALTH LOCUS OF CONTROL SCALE.

Wallston et at 1978

Please circle the number which is most representative of your views in answer to the following questions.

		STRONGLY DISAGREE	DISAGREE	SLIGHTLY DISAGREE	SLIGHTLY AGREE	AGREE	STRONGLY AGREE
a.	If I get sick, it is my own behaviour which determines how soon I get well again.	1	2	3	4	5	6
b.	No matter what I do, if I am going to get sick, I will get sick.	1	2	3	4	5	6
c.	Having regular contact with my doctor is the best way for me to avoid illness.	1	2	3	4	5	6
d.	Most things that affect my health happen to me by accident.	1	2	3	4	5	6
e.	Whenever I don't feel well, I should consult a medically trained professional.	1	2	3	4	5	6
f.	I am in control of my health.	1	2	3	4	5	6
g.	My family has a lot to do with my becoming sick or staying healthy.	1	2	3	4	5	6
h.	When I get sick I am to blame.	1	2	3	4	5	6
i.	Luck plays a big part in determining how soon I will recover from an illness.	1	2	3	4	5	6
j.	Health professionals (e.g. doctors, nurses) control my health.	1	2	3	4	5	6
k.	My good health is largely a matter of good fortune.	1	2	3	4	5	6
l.	The main thing which affects my health is what I myself do.	1	2	3	4	5	6
m.	If I take care of myself I can avoid illness.	1	2	3	4	5	6
n.	Whenever I recover from an illness, it's usually because other people (for example doctors, nurses, family, friends) have been taking good care of me.	1	2	3	4	5	6
o.	No matter what I do, I am likely to get sick.	1	2	3	4	5	6
p.	If it's meant to be, I will stay healthy.	1	2	3	4	5	6
q.	If I take the right actions, I can stay healthy.	1	2	3	4	5	6
r.	Regarding my health, I can only do what my doctor tells me to do.	1	2	3	4	5	6

I.H.L.C. ☐ 20 - 30

P.H.L.C. ☐ 15 - 25

C.H.L.C. ☐ 10 - 20

Reference: Wallston K, Wallston B, DeVillis R, 1978
Development of the Multidimensional Health Locus of Control Scales
Health Education Monograph 6, 160-170

Final Interview of Pill Cycle Manipulation Study

Structured to take approximately one hour.

Volunteer Code Number:_____
Date: _____
Study Week and Day: _____

A) Collect all remaining study materials

B) Briefly review how she has been since the last visit in the same manner as in previous monthly meeting: So how have you been since I last saw you?

C) Pose the following questions and note responses:

1) Have you felt any different since you stopped taking the study pills?

	Physically	Emotionally
Better		
Worse		
No different		
Other comments:		

2) While you were taking the study pills, do you think anything was different physically?

Improved physical symptoms:
Worse physical symptoms:

3) Do you think anything was different mentally or emotionally while you were taking the study pills?

Improved mood symptoms:
Worse mood symptoms:

4) Do you think you were *expecting* to feel differently during the study?

5) Did you feel differently in the way you *expected* to?

6) What happened that you didn't expect?

7) What did you dislike about taking part in the study?

8) Did you dislike not knowing when you were going to bleed?

9) Did you have any irregular bleeding? How did you feel about this?

10) Were you worried that you might become pregnant?

11) What was positive for you about taking part in the study?

12) Would you take part in a similar study again? Why yes or no?

13) Would you recommend to a friend that she take part in this study? Why yes or no?

14) Overall how would you describe your experience?

D) Ask her to fill in a brief written assessment of the study.

E) Go through the assessment with her and explore the areas where verbal and written responses are different.

F) Unblind her. Tell her which group she was in, and briefly explain the reason why the study was carried out. Note her comments once she is unblinded. Thank her for taking part. Explain that the results will be written up, but that confidentiality will be maintained.

Study Assessment

Code Number:_____

Date:_____

1) Please circle the correct reply.

I was / was not worried about the effects that the study would have on me before I started it.

If yes, what were you worried about?

_____
_____
_____
_____
_____

2) Please complete the sentence by circling the words that best describe your experience. While I was in the study-

:I was	more / less / not / no more than usually	bloated
:I had	more / less / no / no more than usual	breast tenderness
:I	did gain / did not gain / stayed the same	weight
:I had	more / fewer / the same number of	headaches
:I was	more / less / no more than usually	bad tempered
:I had	bigger / smaller / no more than the usual	mood swings
:I had	more / less / the same amount of	sexual interest
:I was	more / less / no more than usually	depressed
:I had	heavier / lighter / the same amount of	bleeding
:I had	longer / shorter / the same length	bleeds
:I had	a lot / some / a little / no	breakthrough bleeding or spotting
:I had	more / less / the same amount of	period pain
:I had	more / less / the same amount of	PMS
:I	did / did not experience unexplained	nausea
:I had	more / less / the same amount of	energy
:I was	more / less / no more than usually	happy
:I was	more / less / no more than usually	tense

Please note any other changes which you experienced which are not listed here:

_____
_____
_____
_____

3) Please circle the correct reply.

During the study, I was / was not worried about the effects that it was having on me.

If yes: Which effects worried you most and why?

The effects on my bleeding, because _____
_____
_____
_____
_____
_____
_____

The effects on my physical well being, because_____
_____
_____
_____
_____
_____
_____

The effects on my mood, because_____
_____
_____
_____
_____
_____
_____

Other_____
_____
_____
_____
_____

4) Please complete the following sentence

I am very pleased / am pleased / regret / very much regret that I took part in the study, because_____
_____
_____
_____
_____
_____

Any other comments about the study:

Idealized Models for Detecting the Presence of an Endogenous Infradian Rhythm of Well Being

The following five figures depict some possible patterns of respone to the manipulations in pill cycle length made in the controlled study. Each model is idealized to represent the manifestation of the rhythm based on one possible causal mechanism. The effect that the particular mechanism might have on each study group is shown in succession. The shape of the curve is meant to approximate the shape that one often sees of diary ratings over time. It is an amalgamation of some of the models shown in Figure 5.02. While the principle of the relaxation oscillator is useful, the saw-tooth function is probably not the most accurate visualization of cycle-related change, nor is a cosine curve or an impulse sine wave. The function drawn in these models aims to reflect the speed at which symptoms tend to build up and be released in real time over the cycle.

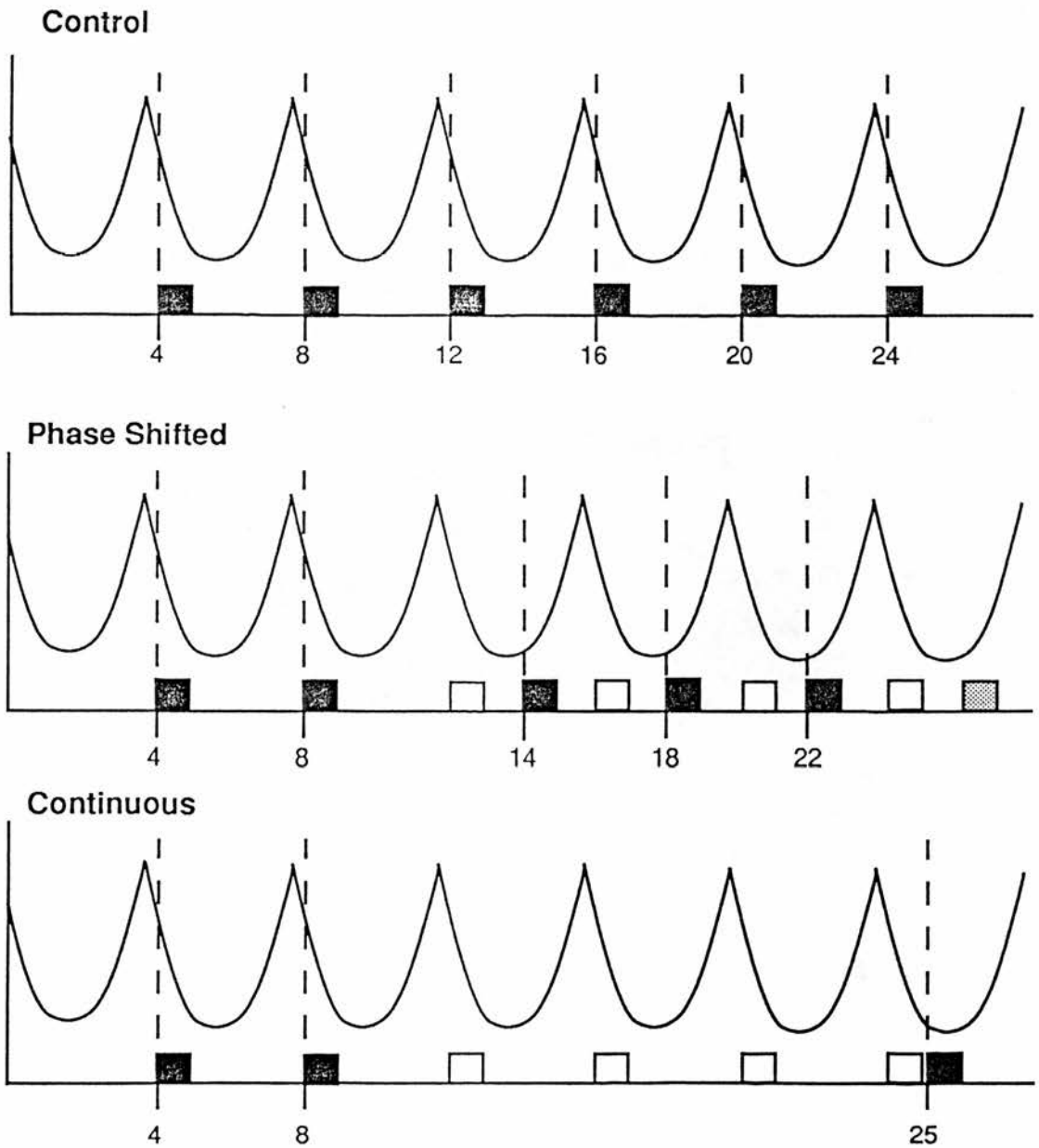
Model 1 shows the symptom pattern that might be expected if the endogenous rhythm were approximately 28 days long, and would free run robustly in spite of disruptions to the steroid cycle. For this to occur the oscillator would have to be very strongly determined with the implication that under normal circumstances the infradian rhythm and the steroid cycle were in coupling, but that the infradian rhythm is not driven by the steroid cycle. Thus the *phase* changes in the phase shifted and continuous groups would not modulate the timing of the purported rhythm. The rhythm is hypothesized to be circa-monthly because of its apparent relationship to the timing of the pill/menstrual cycle, but this need not be the correct *period.* Differences in *period* across individuals may begin to explain the wide varaition one sees in the expression of cycle-related symptoms.

Model 2 explores two ways in which cyclicity may be shown to be steroid dependent. Strictly speaking in figure 2a the peak in symptoms should occur after the withdrawal/fall of steroid hormones. This model implies that changes in well being only posses the endogenous momentum which is given to them by changes in the steroid environment. Therefore it is the sudden withdrawal of steroids in the pill cycle, or the precipitating events and their rapid fall in the menstrual cycle which produce symptoms. A variation on this sort of steroid dependency, shown in 2b, presumes that after a certain duration of either endogenous or exogenous steroids the individual will become symptomatic. This function encorporates the concept of "menstrual release" in which the fall in steroids and/or the physiological events inherent in vaginal bleeding produce a relief from adverse symptoms.

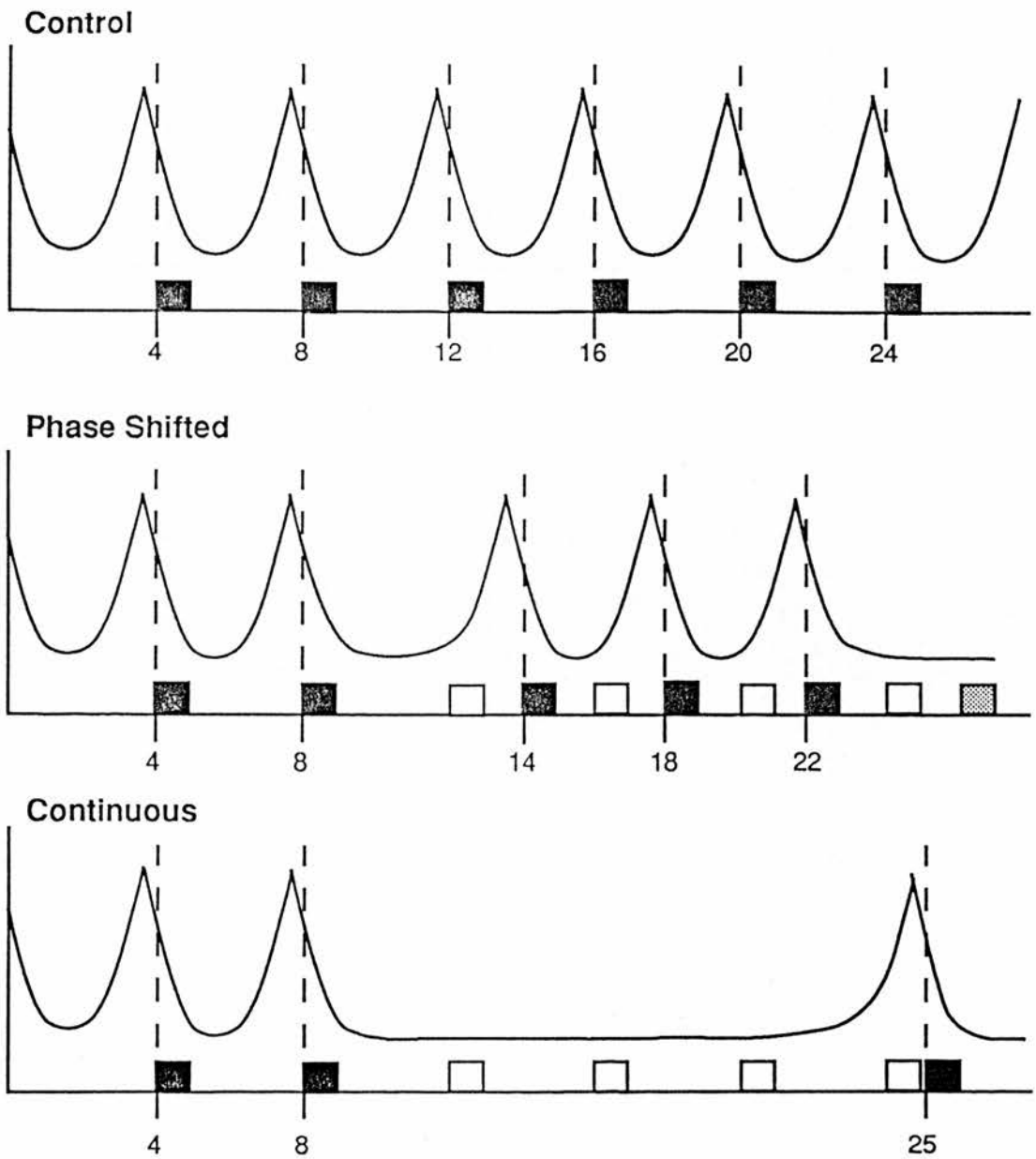
Model 3 also infers a degree of endogenicity. However, in the two variations of this model, the pattern need not be terribly robust, but may be susceptible to a variety of entraining, disruptive, or modulating influences. In this concept the rhythm may only be "borrowing" its momentum from other internal or external rhythmic forces and not posess real in-built drive. Alternatively, it may be a weak internal mechanism which is a "slave oscillation" to a dominant pacemaker. There may even be variation in the amplitude or period of the rhythm from one cycle to the next based on slight variations in the temporal relationship of the infradian rhythm to the forces that are driving it. And, for example, in the continuous group which is experiencing no reinforcement from cycling steroids, the well being oscillator may become damped down over time or show larger than usual changes in its period. Equally one would expect the period and amplitude of the rhythm to be disturbed following the smaller phase disruption in the phase shifted group.

These models are ideals. The actual experience of individual women shows nothing like the uniformity shown in Models 1 and 2 for the control group. There are abundant examples throughout this thesis to demonstrate that. What is more likely than that one model will fully describe the reactions women show to cycle manipulations, is that their responses will be a of compilation of all of these. The only principle that is exclusive would be that steroid hormones determine subjective state in a mechanistic way. However, there is no conclusive evidence to support this idea, and abundant evidence to suggest that it offers inadequate explanation. Further if any one model provided the best fit it should do so consistently within a symptom, and probably across symptoms.

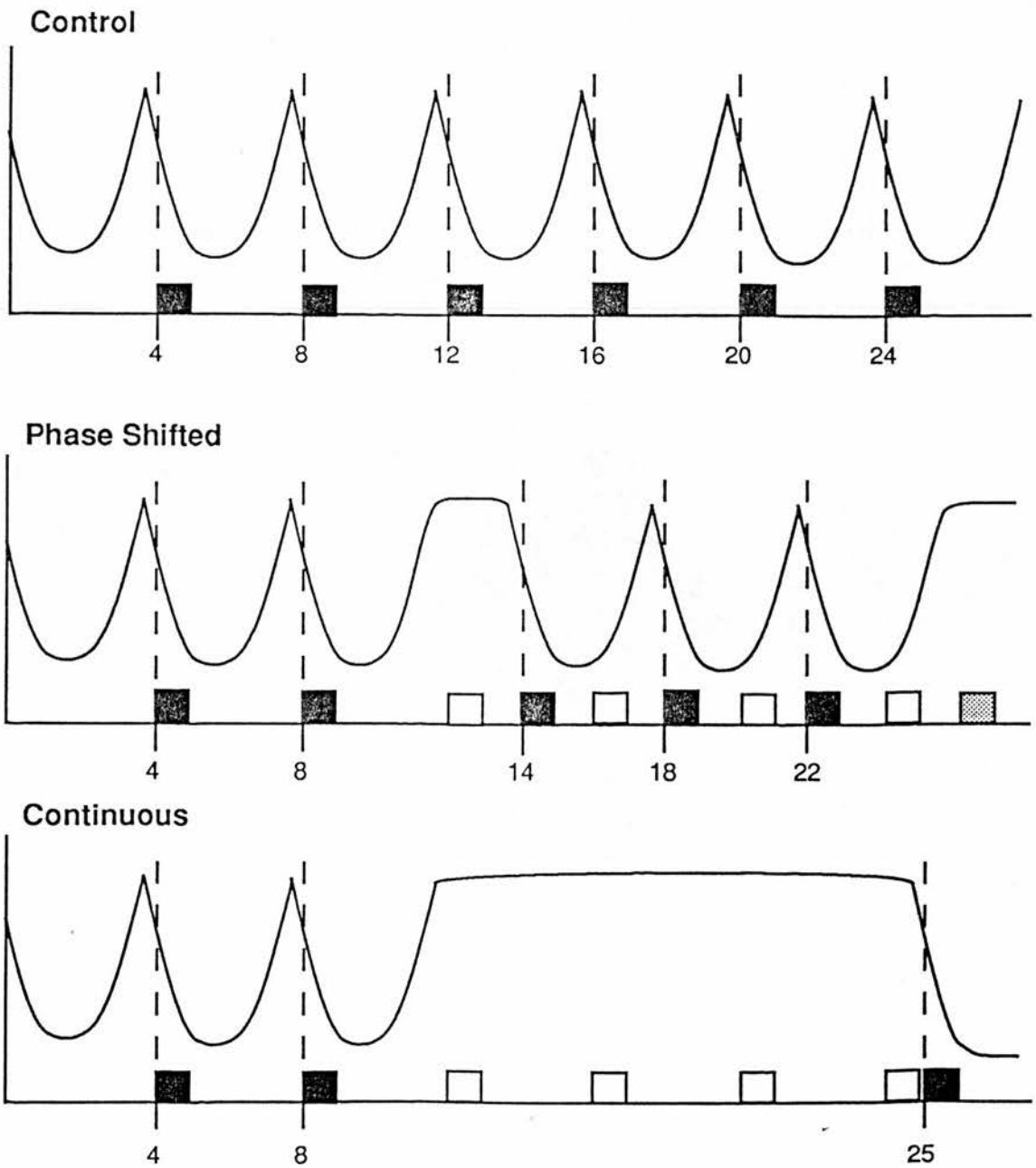
A tracing of each function was over-laid on the profiles of selected symptoms for all women who took part in the cycle manipulation study. No one symptom was uniformly described by a specific model. Only the physical symptoms, breast tenderness, bloating, and period pain showed a slight tendency to be best described by the steroid dependent model 2b. Both mood and physical variables were loosely approximated by other models particularly 3b which describes changes in the frequency of peaks in symptom levels. This is plausible within biological rhythm theory which indicates that weak oscillations may "miss beats" when the timing of the dominant oscillator is interupted. A further possibility which was observed in the dataset is that both steroid determining and endogenous rhythm effects may be operating concurrently. For example, there were instances in the continuous and phase shifted groups when peak levels of symptoms occuring at regular intervals, seemed to be superimposed upon a raised baseline (eg. B12-depression and bloating, A3-breast tenderness). Thus, some of the principles underlying these models do seem to posess a degree of explanatory value, but no one model is adequate on its own. The features of the proposed biological rhythm are discussed further in Chapters Five and Six.



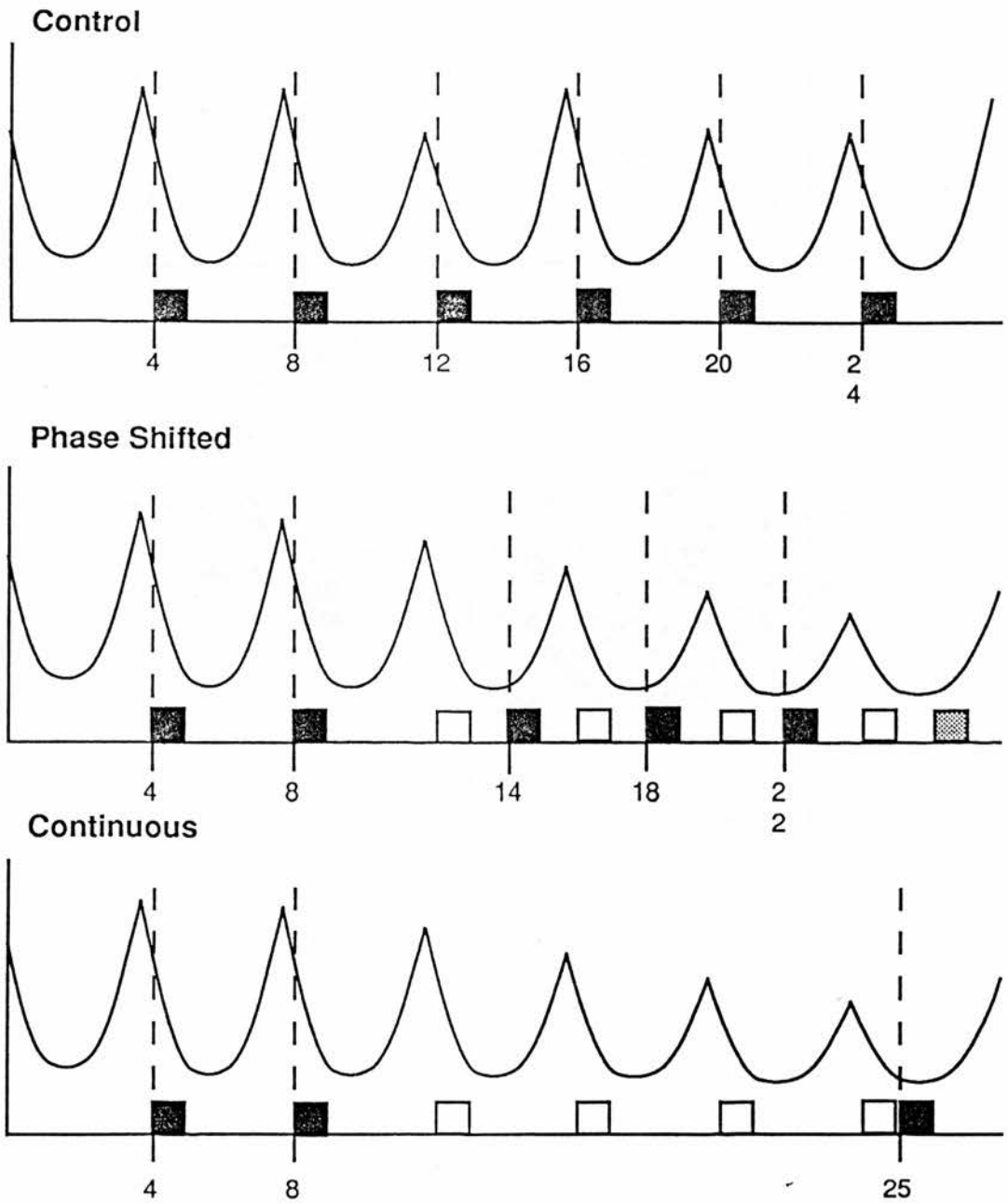
Model 1 - Robust circa 28 day endogenous rhythm



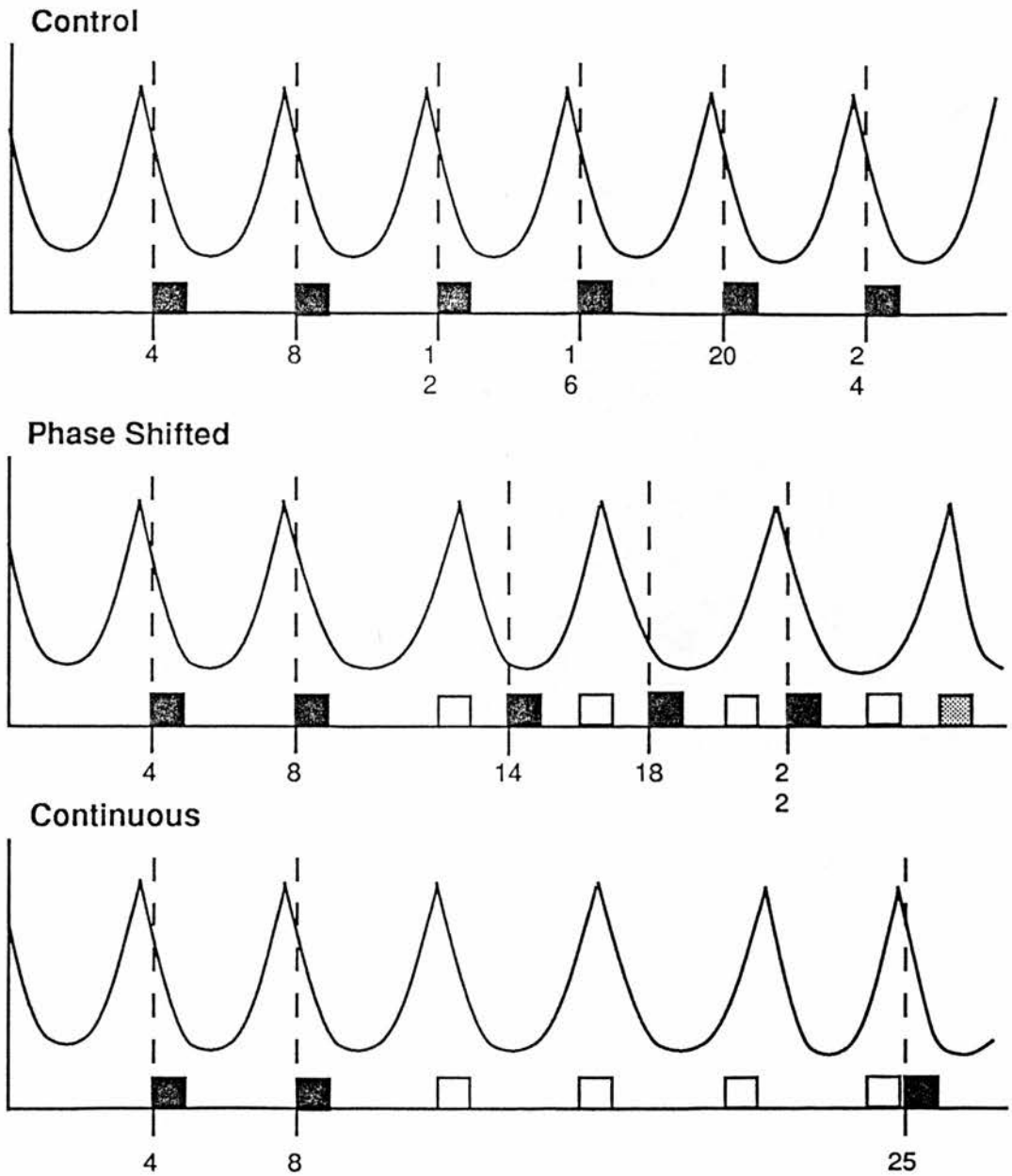
Model 2a - Rhythm based on withdrawal of steroids



Model 2b - Rhythm based on chronic steroids and menstrual release



Model 3a - Weak endogenous rhythm with damped amplitude



Model 3b - Weak endogenous rhythm with variable period

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